

## Hydroxyethyl Starches

### Different Products - Different Effects

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With the development of a new generation of hydroxyethyl starches (HES), there has been renewed interest in their clinical potential. High doses of first- and second-generation HES were associated with adverse effects on renal function, coagulation, and tissue storage, thereby limiting their clinical applicability. Newer HES products have lower molar substitution and *in vivo* molecular weight, resulting in more rapid metabolism and clearance. In this review article, the differences between HES generations are highlighted, with particular emphasis on the improved safety profile of the third generation products. These improvements have been achieved with no loss of efficacy, and they contradict the assumption that efficacy of HES solutions is directly linked to plasma concentration. The impact of source material on structure and pharmacokinetics is highlighted, and the role of the carrier solution is critically assessed.

A RECENT systematic review of randomized clinical studies on the use of fluid therapy in various types of surgical procedures found no evidence to recommend one type of fluid therapy over another. Neither was there sufficient evidence to provide guidance on the optimal amount of fluid to use in elective surgical procedures.<sup>1</sup> It was therefore concluded that guidelines for perioperative fluid management must be procedure-specific; in the absence of firm evidence for one approach or another, individualized, goal-directed fluid administration should be used. Currently, it appears that a restrictive rather than a liberal fluid regimen is beneficial in patients undergoing colorectal surgery. Conversely,

patients suffering from systemic inflammation appear to benefit from “aggressive” fluid replacement, as demonstrated by Rivers *et al.*<sup>2</sup> and as supported by the current sepsis guidelines.<sup>3</sup>

This is in line with the conclusion of Brandstrup, who critically evaluated the evidence behind current standard fluid therapy and the effect of fluid therapy on the outcomes of surgery.<sup>4</sup> The latter author reported that choice of standard fluid therapy is not generally evidence-based and that methodological flaws during attempts to restrict fluid therapy actually result not in restriction, but simply replacement of lost fluids. Therefore, it is recommended to replace lost fluid and avoid fluid overload, which echoes earlier recommendations to adopt goal-directed intraoperative fluid therapy.<sup>5</sup>

Despite the absence of clear recommendations for any particular fluid therapy, there is plentiful debate about the relative merits of crystalloid or colloid, and even about different types of colloids. As recently remarked by Boldt in an editorial, “Researchers who show crystalloid to be superior always find crystalloid superior, whereas colloid supporters always favor colloids.”<sup>6</sup> This review article will not attempt to enter into this debate but will review the current status of knowledge for one type of synthetic colloid, namely the hydroxyethyl starches (HES), with a particular focus on their safety. There have been major developments in this field over recent years, and the newest generation of HES displays significantly different properties in comparison with earlier products. If individualized therapy is to be most effective, it is important to understand what each type of HES offers to the patient.

### Development of HES: Hetastarch to Tetrastarch

The first HES product, *i.e.*, Hespan<sup>®</sup> (DuPont Pharmaceuticals, Wilmington, DE), was made available in the United States in the 1970s. Since then, further generations of HES have been developed, differing in their mean molecular weight (MW), molar substitution (MS), and C<sub>2</sub>/C<sub>6</sub> ratio. Hydroxyethyl starches are identified by three numbers, *e.g.*, 10% HES 200/0.5 or 6% HES 130/0.4.

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**Table 1. Characteristics of Hydroxyethyl Starch (HES) Preparations**

	Concentration and Solvent	Mean Molecular Weight, kDa	Molar Substitution	C <sub>2</sub> /C <sub>6</sub> Ratio	Maximum Daily Dose, ml/kg
HES 670/0.75	6% balanced solution	670	0.75	4.5:1	20
HES 600/0.7	6% saline	600	0.7	5:1	20
HES 450/0.7	6% saline	480	0.7	5:1	20
HES 200/0.62	6% saline	200	0.62	9:1	20
HES 200/0.5	6% saline	200	0.5	5:1	33
	10% saline				20
HES 130/0.42	6% saline	130	0.42	6:1	50
HES 130/0.42	6% balanced solution	130	0.42	6:1	50
	10% balanced solution				33
HES 130/0.4	6% saline	130	0.4	9:1	50
	10% saline				33
HES 130/0.4	6% balanced solution	130	0.4	9:1	50
HES 70/0.5	6% balanced solution	70	0.5	3:1	20

Data sources: Kozek-Langenecker *et al.*<sup>39</sup> and Boldt *et al.*<sup>104</sup>

The first number indicates the concentration of the solution, the second represents the mean MW expressed in kiloDalton (kDa), and the third and most significant one is MS. These parameters are highly relevant to the pharmacokinetics of HES (table 1).

#### Concentration

Concentration mainly influences the initial volume effect: 6% HES solutions are iso-oncotic *in vivo*, with 1 l replacing about 1 l of blood loss, whereas 10% solutions are hyperoncotic, with a volume effect considerably exceeding the infused volume (about 145%).<sup>##</sup>

#### Molecular Weight

In common with all of the synthetic colloids, HES are polydisperse systems containing particles with a wide range of molecular mass. In polydisperse systems, the determination of particle mass or relative molecular mass gives averages, which depend on the method used. The MW can be described in one of two ways: weight averaged MW ( $M_w$ ) and number averaged MW ( $M_n$ ).

Number average MW ( $M_n$ ) is calculated as:

$$M_n = \frac{\sum n_i M(i)}{\sum n_i}$$

The weight averaged (or mass averaged) MW ( $M_w$ ) is calculated as:

$$M_w = \frac{\sum n_i \{M(i)\}^2}{\sum n_i M(i)}$$

where  $n_i$  and  $M(i)$  are the amount of substance and the relative molecular mass of the species  $i$ , respectively.

The weight-averaged MW is more influenced by the larger molecules in the system and gives a larger value

for the averaged MW than the number averaged MW. The ratio  $M_w/M_n$  gives an index of the degree of polydispersity in the system. When a polydisperse colloid is infused into the circulation, small molecules below the renal threshold (45 to 60 kDa<sup>7</sup>) are rapidly excreted, whereas the larger molecules are retained for varying periods of time depending on their size and ease of breakdown. However, osmotic effectiveness depends on the number of particles, and not the molecular size; therefore, the excretion of the smaller particles continuously reduces the osmotic effectiveness of the infused solution. This is compensated for by the continuous supply of oncologically active molecules arising from degradation of larger fragments. Mean MW of the available products ranges from over 670 kDa to 70 kDa (table 1). However, the physicochemical properties, metabolism, and excretion are predominantly influenced by the MS and the pattern of substitution. *In vitro* MW has little impact on plasma accumulation, but significant pharmacokinetic differences can be noticed between HES products with the same MW but different MS, *e.g.*, HES 200/0.62 and HES 200/0.5.<sup>8</sup>

#### Molar Substitution

HES have a varying number of hydroxyethyl residues attached to the anhydrous glucose particles within the polymer. This substitution increases the solubility of the starch in water and, to a varying degree, inhibits the rate of destruction of the starch polymer by amylase. As with MW, there are two methods for calculating the degree of substitution on the starch polymer. The first of these is termed the degree of substitution and is calculated from the number of substituted anhydroglucose residues divided by the total number of anhydroglucose residues:

$$DS = \frac{G_s}{G_t}$$

where DS represents the degree of substitution,  $G_s$  the number of substituted anhydroglucose residues, and  $G_t$

<sup>#</sup> SmPC Hemohes 10%. Available at: www.fachinfo.de. Accessed May 15, 2009.

<sup>\*\*</sup> SmPC HAES-Steril 10%. Available at: www.fachinfo.de. Accessed May 15, 2009.

the total number of anhydroglucose residues in the polymer. The second is generally referred to as the MS, which is calculated as the average number of hydroxyethyl groups reacted per anhydroglucose residue. This may be calculated from the following formula:

$$MS = \frac{W_H}{1 - W_H} \times \frac{162}{44}$$

where  $W_H$  is the weight fraction of hydroxyethyl groups in the polymer. The numbers represent the mass of the hydroxyethyl group (44) and the anhydrous glucose residue, (162) respectively. More than one substitution can occur on each anhydroglucose residue; therefore, this calculation generally gives a higher value than the degree of substitution. MS is thus the average number of hydroxyethyl residues per glucose subunit. The figure 0.7 in the description of a HES preparation indicates that there are seven hydroxyethyl residues on average per 10 glucose subunits. Starches with this level of substitution are called hetastarches, and similar names are applied to describe other levels of substitution: hexastarch (MS = 0.6), pentastarch (MS = 0.5), and tetrastarch (MS = 0.4). Unsubstituted anhydroglucose units are more prone to enzymatic degradation by  $\alpha$ -amylase; therefore, hydroxyethylation slows down the rate of enzymatic breakdown of the HES molecule and prolongs intravascular retention time. As will be shown below, older generation HES products with high MS accumulate in the plasma, unlike the latest generation of tetrastarches.

#### $C_2/C_6$ Ratio

The *pattern* of hydroxyethylation also has a significant impact on the pharmacokinetic properties, but this may not be appreciated because it does not appear in the usual product specification alongside MW and MS. Hydroxyethylation of the glucose subunits is guided predominantly towards the  $C_2$  and  $C_6$  carbon atoms (fig. 1).

Hydroxyethyl groups at the position of the  $C_2$  atom inhibit the access of  $\alpha$ -amylase to the substrate more effectively than do hydroxyethyl groups at the  $C_6$  position.<sup>9</sup> Hence, HES products with high  $C_2/C_6$  ratios are expected to be more slowly degraded. In a study by Jung *et al.*,<sup>10</sup> two HES solutions with similar MW and MS (HES

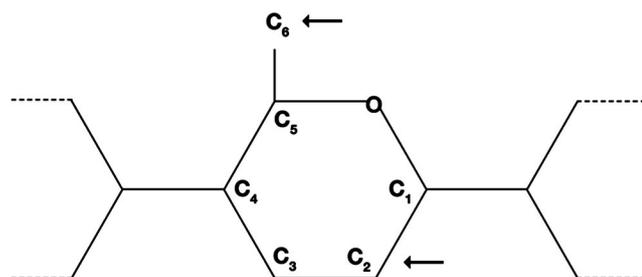


Fig. 1. Hydroxyethyl substitution of hydroxyethyl starch (HES) glucose subunits takes place preferentially at the  $C_6$  and  $C_2$  positions.

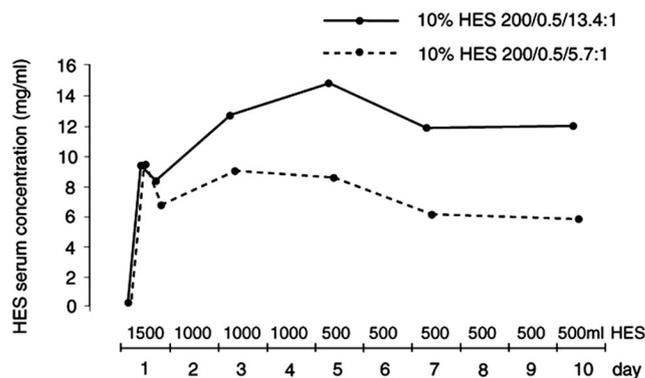


Fig. 2. Different effects on serum concentration during 10-day hemodilution therapy of two pentastarches with different  $C_2/C_6$  ratios: 10% hydroxyethyl starch (HES) 200/0.5/13.4:1 and 10% HES 200/0.5/5.7:1. (Comparison between the two HES preparations from the third timepoint on day 1 is  $P < 0.01$ ). Reprinted with permission from Treib J, *et al.*<sup>11</sup>

200/0.5) but different  $C_2/C_6$  ratios were compared in six volunteers. Notably, the area under the plasma concentration curve was larger in the group receiving the product with the higher  $C_2/C_6$  ratio, confirming that a higher  $C_2/C_6$  ratio decreases hydrolysis by  $\alpha$ -amylase. The duration of hemodilution was also greater in this group.

A study by Treib *et al.*<sup>11</sup> in patients with cerebrovascular disease also compared two pentastarches (10% HES 200/0.5), differing only in their  $C_2/C_6$  ratios. The plasma concentration was lower from day 3 onwards in the group receiving the HES with the lower  $C_2/C_6$  ratio (fig. 2), and the *in vivo* MW in plasma decreased much more with this HES solution.

A number of studies in volunteers and in patients undergoing cardiac and noncardiac surgery clearly demonstrate how these structural differences between the distinct generations affect pharmacokinetic properties.

#### Pharmacokinetic Studies

Published pharmacokinetic data for various types of HES solution are summarized in tables 2 and 3 and in figure 3. Studies reveal that accumulation of more highly substituted HES products is much greater than that of the tetrastarches. Clearance of earlier HES products is much slower, with the result that first and second generation HES products are not completely eliminated from the circulation within 24 h.<sup>8,12</sup> Repeated infusions lead to steadily accumulating residual HES in the plasma.

A study of single doses in healthy volunteers<sup>13</sup> strikingly illustrated the effect that high MS (0.75) has on plasma clearance. Plasma clearance of HES 670/0.75 (Hextend®; Hospira Inc., Lake Forest, IL) was 0.98 ml/min, and initial half-life was 6.3 h, increasing to 46.4 h for the first 7 days. Similar characteristics were found by Yacobi *et al.*<sup>14</sup> by using hetastarch in a saline carrier.

Plasma accumulation of hetastarch was noted by Mishler *et al.*<sup>15</sup> after repetitive dosing in healthy volunteers. After three infusions of a relatively low dose of

**Table 2. Pharmacokinetics of Different Hydroxyethyl Starches (HES) after a Single Dose in Healthy Volunteers**

	Dose, g	C <sub>max</sub> , mg/ml	T <sub>1/2α</sub> , hours	T <sub>1/2β</sub> , hours	T <sub>1/2central</sub> , hours	AUC (infinity), mg · ml <sup>-1</sup> · h <sup>-1</sup>	Clearance, ml/min	Infusion Time, min
HES 670/0.75 (6%) <sup>13</sup>	0.6/kg	13	6.3*	46.4†	na	926.0	0.98	20‡
HES 450/0.7§ (6%) <sup>14</sup>	30	7.8	na	300	na	na	na	60
HES 200/0.62 (6%) <sup>12</sup>	30	5.2	5.08	69.7	44.42	na	1.23	30
HES 200/0.5 (6%)	30	6	na	na	na	na	4.88	15
HES 200/0.5 (10%) <sup>12</sup>	50	8.0	3.35	30.6	7.12	na	9.24	30
HES 130/0.4 (6%) <sup>19</sup>	26.3	3.7	1.39#	12.1#	1.55	14.3	31.4	30
HES 130/0.42 (6%) <sup>34</sup>	60	10.10		12.0142		58**††	19	30
HES 130/0.4 (10%) <sup>19</sup>	44.1	6.5	1.54#	12.8#	1.82	28.8	26.0	30

Data source: Lehmann *et al.*,<sup>34</sup> Jungheinrich *et al.*,<sup>138</sup> and Tetraspan SmPC (††SmPC Tetraspan 6%; available at www.fachinfo.de; accessed May 2009.)

\* Mean for 0 to 8 hr; † mean for 7 to 10 days; ‡ calculated for 70 kg bodyweight; § product label declaration, however, actually 670/0.75; || for days 7 to 28 after treatment; # model independent; \*\* determined after infusion of 1,000 ml; all other studies used 500 ml.

AUC = area under the plasma concentration curve; C<sub>max</sub> = maximum plasma concentration; na = value not stated in source publication; T<sub>1/2α</sub> = initial/distribution half-life; T<sub>1/2β</sub> = terminal/elimination half-life; T<sub>1/2central</sub> = elimination half-life from the central compartment.

30 g (6% HES 450/0.7), the residual HES plasma concentration 24 h after the final infusion was higher than the peak plasma concentration after the first infusion (fig. 3A).

#### Studies of the Pharmacokinetics of Hexastarch and Pentastarch

After a single 500-ml dose in volunteers, the plasma half-life for a more rapidly metabolizable pentastarch (10% HES 200/0.5) was shorter at 3.35 h than the 5.08 h plasma half-life of a hexastarch (6% HES 200/0.62).<sup>12</sup> Clearance was 1.23 ml/min for hexastarch, and 9.24 ml/min for the pentastarch, both of which were faster than the 0.98 ml/min reported above<sup>13</sup> for hetastarch (HES 670/0.75). There were significant differences also in the terminal half-life: 70 h for hexastarch (HES 200/0.62) versus 31 h for pentastarch (HES 200/0.5).

Askali and Förster investigated the same products after five daily doses of 500 ml in volunteers and found significant plasma accumulation for both from the second day, with higher accumulation for the hexastarch solution (fig. 3B). Twenty days after infusion, plasma concentration of the pentastarch was below 0.5 mg/ml, but it was still 1.3 mg/ml 30 days after infusion of the hexastarch.<sup>8</sup>

Lehmann *et al.*,<sup>7</sup> investigating the low-molecular weight pentastarch 6% HES 70/0.5, and found similar plasma accumulation (fig. 3C) to that reported by Asskali and Förster<sup>8</sup> for HES 200/0.5 after repetitive use in volunteers for 5 days. This confirms the importance of MS over MW on pharmacokinetics.

In a clinical study in patients with peripheral artery disease, Költringer *et al.*<sup>16</sup> reported a rise in plasma concentration of 6% HES 200/0.62 over 12 days. In another study using daily infusions of a range of products (hexastarch 6% HES 200/0.62, pentastarch 10% HES 200/0.5, and pentastarch 6% HES 40/0.5) in 30 patients with cerebrovascular disease, intravascular accumulation of all HES types used was noted after repeated infusion.<sup>17</sup> Krömer *et al.*<sup>18</sup> also reported accumulation of pentastarch HES 200/0.5 (10%) after repetitive infusions over 10 days in ischemic stroke patients.

#### Studies of the Pharmacokinetics of Tetrastarch

The third generation of HES, the tetrastarches, were developed with lower MS (0.4) to enhance degradation and to minimize retention in the circulation and tissues.

**Table 3. Pharmacokinetics and Residual Plasma Concentrations of Different HES after Multiple Infusions in Healthy Volunteers**

	Cumulative Dose, g	Treatment Period, d	Plasma Concentration 24 h after last Administration, mg/ml	Clearance, ml/min	T <sub>1/2α</sub> , hours	T <sub>1/2β</sub> , hours	T <sub>1/2central</sub> , hours	AUC, mg · ml <sup>-1</sup> · h <sup>-1</sup>	
								Day 1	Last Day*
HES 450/0.7 <sup>15</sup>	90	3 (3 × 30 g)	9.6	<1	na	na	na	na	>>day 1
HES 200/0.62† <sup>8</sup>	150	5 (5 × 30 g)	7.8	0.983‡	0.568	11.6	211	508	>>day 1
HES 200/0.5† <sup>8</sup>	250	5 (5 × 50 g)	3.4	4.86‡	0.389	6.98	113	171	>>day 1
HES 200/0.5 <sup>139</sup>	250	5 (5 × 50 g)	3.4	na	na	na	na	62.6	96.2
HES 130/0.42 <sup>140</sup>	250	5 (5 × 50 g)	0.7	na	3.81**	na	na	28.41	36.57
HES 130/0.4 <sup>20</sup>	500	10 (10 × 50 g)	<0.5	22.8§	1.14	9.1	na#	32.8	35.7
HES 70/0.5 <sup>7</sup>	250	5 (5 × 50 g)	3.0	na	na	na	na	na	>>day 1

\* Day 3, 5, or 10 according to length of treatment; † three-compartment modeling; ‡ taking days 1 to 5 into account; § day 1: 23.7; day 10: 21.8; || means from days 1 and 10; # not applicable for two-compartment modeling used, and three-compartment modeling would yield a value of 33 h; \*\* only one figure for elimination half-life on day 1 is given; elimination half-life on day 5 increased to 4.72.

AUC = area under the plasma concentration curve; C<sub>max</sub> = maximum plasma concentration; na = value not stated in source publication; T<sub>1/2α</sub> = initial/distribution half-life; T<sub>1/2β</sub> = terminal/elimination half-life; T<sub>1/2central</sub> = elimination half-life from the central compartment.

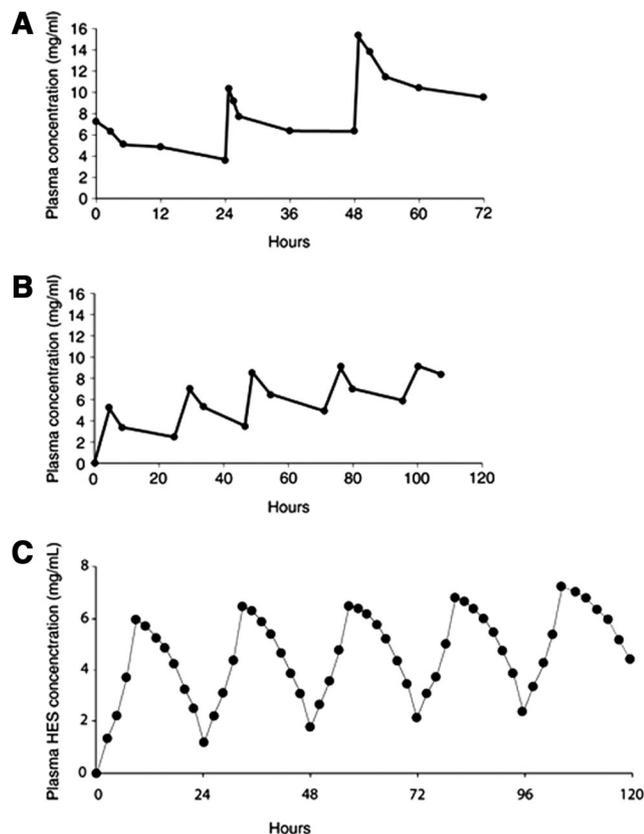


Fig. 3. Plasma accumulation after multiple dosing of (A) 6% hydroxyethyl starch (HES) 450/0.7 (500 ml/d for 3 d); reprinted with permission from Jungheinrich *et al.*<sup>138</sup> (B) 6% HES 200/0.62 (500 ml/d for 5 d); reprinted with permission from Asskali *et al.*<sup>8</sup> (C) 6% HES 70/0.5; reprinted with permission from Lehmann *et al.*<sup>7</sup>

A study by Waitzinger *et al.*<sup>19</sup> using single 500-ml doses of HES 130/0.4 in 12 volunteers found high plasma clearances of 31.4 ml/min for a 6% solution, and 26.0 ml/min for a 10% solution (*vs.* 0.98 ml/min reported for hetastarch by Wilkes *et al.*<sup>13</sup>). Initial elimination half-lives were 1.39 and 1.54 h, respectively, and terminal half-lives were 12.1 and 12.8 h, respectively. This can be compared with the initial elimination half-life of 8.58 h reported by Asskali and Förster<sup>8</sup> for hexastarch in their multiple-dosing studies.

After multiple dosing of ten daily 500-ml infusions (10% HES 130/0.4<sup>20</sup>), initial and final elimination curves were virtually identical, in sharp contrast to those found for hetastarch (6% HES 450/0.7)<sup>15</sup> and hexastarch (6% HES 200/0.62).<sup>8</sup> Maximum plasma concentration, area under the plasma concentration curve, and clearance were virtually identical after the first and the last infusions, indicating no significant plasma accumulation for 10% HES 130/0.4.

Overall, these dosing studies show that clearance of tetrastarch (10% HES 130/0.4) is at least 23 times higher than that of hexastarch (6% HES 200/0.62) or hetastarch (6% HES 450/0.7) and almost five times as high as that of pentastarch (10% HES 200/0.5<sup>21</sup>). These findings have

been confirmed in patients undergoing orthopedic surgery.<sup>22</sup> By the end of the first postoperative day, plasma concentrations of 6% HES 130/0.4 were 1.0 mg/ml compared to 2.6 mg/ml for 6% HES 200/0.5.

#### Effects of Molecular Structure on Efficacy

At first glance, it may seem surprising that plasma persistence is not necessarily related to volume efficacy. Although studies have found significant residual plasma concentrations of highly substituted HES products,<sup>13,14</sup> volume effects beyond 24 h were not detected.<sup>13,15,23,24</sup> Although tetrastarch (HES 130/0.4) displays minimal plasma accumulation, many studies have established that the duration of effect is comparable to that of pentastarch (HES 200/0.5)<sup>25–28</sup> and hetastarch at similar concentrations (6% HES 650/0.7, Hextend<sup>®</sup> or 6% HES 670/0.75 in saline).<sup>29,30</sup>

These results are supported by a number of prospective, randomized, double-blind studies comparing the volumes of 6% HES 130/0.4 and 6% HES 200/0.5<sup>22,31,32</sup> or 6% HES 670/0.75<sup>30</sup> necessary for hemodynamic stabilization during and after cardiac and noncardiac surgery. In all of these studies, the need for infusion was assessed by using predefined hemodynamic, and clinical parameters as infusion triggers and solutions were provided in a blinded fashion. Notably, the volumes of HES required were not significantly different in cardiac surgery,<sup>31</sup> in orthopedic surgery,<sup>22,30,32</sup> and clinical outcomes in all groups were comparable.

Clearance and residual concentrations of HES are closely related to MS and the C<sub>2</sub>/C<sub>6</sub> ratio, whereas colloid oncotic pressure depends on the number of oncologically active particles available and not directly on HES concentration.<sup>21</sup> In a given volume of HES solution, there will be more molecules of a lower MW product than of a HES with a high MW, thus the lower MW product is likely to exert a greater colloid osmotic pressure at a similar plasma concentration (fig. 4A). The *in vivo* MW of HES 130/0.4 is significantly lower compared to HES 200/0.5; therefore, more macromolecules per gram of HES are available to exert a volume effect.

After intravenous infusion, HES molecules that are smaller than the renal threshold (*i.e.*, 45–60 kDa) are excreted, and larger molecules are enzymatically degraded by  $\alpha$ -amylase into progressively smaller fragments until the renal threshold for excretion is reached. HES with low MS are broken down more readily, providing a greater concentration of oncologically active particles more rapidly. A small amount of HES diffuses into the interstitial space, redistributes, and is eliminated, and a further fraction is taken up by the reticuloendothelial system, where it is slowly broken down. Thus, the degree of plasma and tissue accumulation is highly dependent on structure, the specific HES type, and its physicochemical properties.

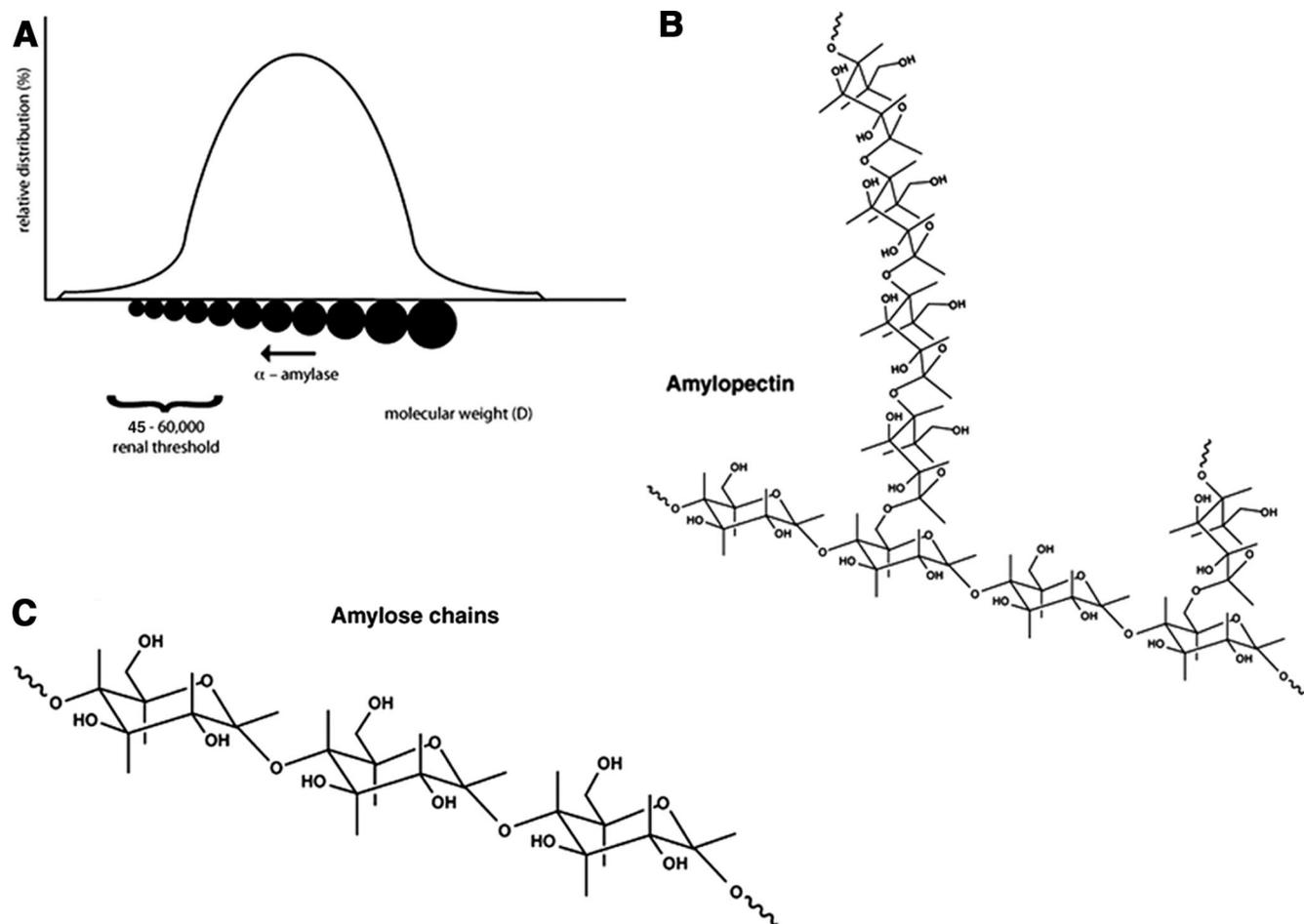


Fig. 4. (A) Hydroxyethyl starch (HES) molecules are steadily reduced over time as a result of enzymatic cleavage with amylase. At any one point in time, there is a range of molecules of different sizes. (B) Difference in structure between amylopectine (branched chains) and amylose (C) amylose (long chains).

#### Effects on Clinical Safety

It is important to consider the data for individual products and not to extrapolate reports from one HES type to another. Clinical studies have revealed significant differences between the HES generations regarding coagulation, tissue storage, and renal function, which are discussed in detail in the following section.

#### Third-Generation HES: Tetrastarch

The development of newer starch-based plasma volume expanders has been driven by a need to improve safety and pharmacological properties while maintaining the volume efficacy of previous HES generations. Reductions in MW and MS have led to products with shorter half-lives, improved pharmacokinetic and pharmacodynamic properties,<sup>33</sup> and fewer side effects.<sup>33</sup> Although earlier products were derived from amylopectin extracted from waxy maize starch, it is inaccurate to refer to HES as if they were only one homogenous product because modifications to MW and the degree and pattern of substitution result in distinct and observable differ-

ences between and within the different generations of HES.

The same is true for starches of similar structure that have been derived from different source materials: waxy maize and potato. Two third-generation starches based on these two materials are currently available in various formulations. According to one study, potato and waxy maize-derived HES solutions are not bioequivalent.<sup>34</sup> Therefore, findings obtained from studies using one type may not be valid for the other.

#### Structural Differences and Bioequivalence

Waxy maize starch (HES 130/0.4) is largely composed (approximately 98%) of highly branched amylopectin (fig. 4B), and potato starch (HES 130/0.42) is a heterogeneous mixture of around 75% of amylopectin, the remainder being linear chains of amylose. The degree of branching is therefore lower in potato starch (fig. 4C).<sup>35</sup>

Potato starches contain several thousand parts per million (ppm) of esterified phosphate groups, and almost none can be detected in waxy maize starch.<sup>36</sup> These differences are carried through to the refined product (table 4). Both starches have comparable MS (0.4 for

**Table 4. Physicochemical Differences between Waxy Maize–derived Hydroxyethyl Starch (HES) 130/0.4 and Potato-derived HES 130/0.42**

	Waxy Maize Starch–based HES 130/0.4	Potato Starch–based HES 130/0.42*
Molar substitution	0.41	0.45–0.46
C <sub>2</sub> /C <sub>6</sub> ratio	9.05:1	6.9–7.7
Degree of branching	6.6 mol%	4.8–5.1 mol%
Free phosphate	—	34–84 ppm
Total phosphate	15 ppm	205–290 ppm
Viscosity (Mark Houwink) constants	K = 2.29 × 10 <sup>-3</sup> A = 0.353	K = 2.73 – 3.52 × 10 <sup>-3</sup> A = 0.329 – 0.348

\*Ranges reflect values obtained from different batches.

Data source: Sommermeyer *et al.*<sup>33</sup>

PPM = parts per million.

waxy maize *vs.* 0.42 for potato), although Sommermeyer *et al.* suggest that the MS of the potato-derived product actually approaches 0.45.<sup>33</sup>

The waxy maize–derived HES 130/0.4 (Voluven®; Fresenius Kabi, Bad Homburg, Germany) has a C<sub>2</sub>/C<sub>6</sub> ratio of about 9:1 as compared to a ratio of 6:1 for the potato-derived starches 130/0.42 (Venofundin®; B Braun, Melsungen, Germany), Vitahes® (Serumwerk Bernburg; Bernburg, Germany) or PlasmaVolume Redibag® (Baxter, Unterschleißheim, Germany). As has been shown with earlier-generation HES preparations, a higher C<sub>2</sub>/C<sub>6</sub> ratio should in part counteract hydrolysis by  $\alpha$ -amylase.

Sommermeyer *et al.* also established that potato starch–derived HES has a higher intrinsic viscosity than waxy maize–derived starch of the same MW,<sup>33</sup> which most likely results from the difference in degree of branching. Unfortunately, not much is known about the effects of this increase in viscosity. Currently, the clinical implications are unclear and require further investigation.

These structural differences, however, may affect pharmacokinetic properties. In this context, Lehmann *et al.* found significant differences in the total apparent clearance of these two products and a higher area under the plasma concentration curve for the waxy maize–derived product (HES 130/0.4), demonstrating that the products are not bioequivalent.<sup>34</sup> Degradation and elimination should occur more rapidly in the polymer with the lower MS (*i.e.*, the HES 130/0.4 product) but Lehmann suggested that the higher C<sub>2</sub>/C<sub>6</sub> ratio of 9:1 hydroxyethylation at the second carbon atom (C<sub>2</sub>) effectively inhibits access of  $\alpha$ -amylase, thus retarding degradation.

### Safety Profile

**Tetrastarches: Effects on Coagulation and Platelet Function.** A number of studies have investigated the *in vitro* and *in vivo* effects of various HES products on coagulation and platelet function. Overall, the more rapidly degradable HES products have been found to have a

greatly reduced effect on the coagulation process compared to older products.<sup>37,38</sup>

HES macromolecules interact with platelets and the coagulation cascade, causing a decrease in factors such as Factor VIII and von Willebrand factor, but the exact mechanisms have still not been fully elucidated.<sup>39</sup> There have been consistent reports of coagulation impairment since slowly degradable HES preparations were introduced into clinical practice. These HES preparations decreased circulating plasma concentrations of coagulation factors in volunteers and patients, even when used below the recommended maximum doses.<sup>30,38,40–44</sup> Details of maximum doses of some HES products can be found in table 1.

Treib *et al.* carried out systematic studies on the effects of a range of HES preparations and found that the products with higher MS had a profound effect on coagulation and platelet function but suggested that newer HES preparations should only have minimal effects.<sup>11,17</sup> In a study on 30 patients with cerebrovascular disease,<sup>17</sup> patients were randomized to receive daily infusions with up to 1.5 l of 6% HES 200/0.62, 10% HES 200/0.5, or 6% HES 40/0.5. Platelet count was significantly decreased in all three groups, but the largest drop was seen in the HES 200/0.62 group. The authors speculate that HES macromolecules attach to platelets or are phagocytized by them. Larger platelets are broken down, and more thrombocytes are released in compensation.

*In vitro* studies of the coagulation process seem to agree that the altered pharmacokinetics of the newer generation of HES preparations have led to products with improved effects on coagulation and platelet function.<sup>41,45–47</sup> However, *in vitro* studies have limitations and may be misleading in that, in the absence of the normal compensatory mechanisms, at least part of the observed effects may be attributable to simple hemodilution or to the presence of calcium in the solvents.<sup>48,49</sup>

Furthermore, *in vitro* assays cannot mimic the *in vivo* physiologic reactions that take place during progressive hemodilution. At 1–2 h after infusion, von Willebrand factor reaches its minimum, exceeding the degree of dilution and indicating that additional mechanisms play a part in the process.<sup>41</sup> The endothelium plays an important role in the coagulation cascade, but it is absent from *in vitro* studies. Also, large amounts of crystalloids are often given, in addition to, during surgery, and surgery itself has an impact through surgically caused injury.

The most useful evidence concerning the safety of waxy maize-derived 6% HES 130/0.4 is derived from extensive clinical studies in many types of major surgery. Although very high doses have been used,<sup>50</sup> no adverse effects on coagulation have been reported compared to controls using lower doses.

In one high-dose study, Ellger *et al.*<sup>51</sup> found that 6% HES 130/0.4, when given up to 50 ml/kg, had similar effects on coagulation as 30 ml/kg HES 200/0.5 plus

gelatin. In this study, 40 patients undergoing elective surgery for urology-related cancer were randomized to receive one of the HES preparations. Coagulation parameters were measured at five time points during and after surgery. The authors noted that there was some deterioration of coagulation during surgery but that this was most likely the result of blood loss and hemodilution. No significant differences were found between groups in terms of hemoglobin, hematocrit, platelet count, coagulation factors (prothrombin time, partial thromboplastin time, von Willebrand factor, Factor VIIIc) or blood loss.

Similar results were obtained in a study of 120 patients undergoing elective coronary artery bypass surgery.<sup>52</sup> Patients were randomized to volume replacement either with 6% HES 130/0.4 (up to 50 ml/kg) or 6% HES 200/0.5 (up to 33 ml/kg) with volume requirements in excess of these doses being met with gelatin. Despite being used at a median dose of 49 ml/kg, HES 130/0.4 did not increase blood loss and transfusion requirements compared to the lower dose of HES 200/0.5. The authors also noted that patients randomized to be treated with pentastarch received three times as much gelatin as those in the tetrastarch group and speculated that this should, if anything, have biased this group towards reduced blood loss.

In patients with severe head injury, a strategy of aggressive fluid resuscitation is widely used with the aim of achieving a high cerebral perfusion pressure. In line with this concept, Neff *et al.*<sup>50</sup> administered very high doses of HES 130/0.4 to 31 patients with severe head injury, up to 70 mg/kg or a control 6% HES 200/0.5 up to a limit of 33 mg/kg followed by albumin up to a total dose of 70 mg/kg if further volume was required. Coagulation factors often rise above normal values after trauma, and this reaction is usually suppressed by older HES products. The authors found no major differences in coagulation variables but noted that, at various time points up to day 6, there was less suppression of Factor VIII, von Willebrand factor, and ristocetin cofactor by the tetrastarch, despite the large doses administered.

A pooled analysis<sup>53</sup> of prospective and randomized studies comparing 6% HES 130/0.4 with 6% HES 200/0.5 in patients undergoing major surgical procedures (n = 449) was carried out by Kozek-Langenecker *et al.*<sup>22,26,31,32,54</sup> The authors concluded that HES 130/0.4 was associated with a significant reduction in perioperative blood loss, both estimated and calculated, and that there was a significant reduction in transfusion needs. The reduction in the volume of erythrocyte loss and in transfusion needs was in the order of one red blood cell unit for both parameters (table 5).

A meta-analysis including 73 randomized trials compared the clinical outcome in adult patients receiving colloids in the perioperative period.<sup>55</sup> HES were stratified according to MS. It was found that tetrastarches were associated with a 15% reduction in blood loss compared to gelatin and pentastarches. Pentastarches

**Table 5. Pooled Analysis of Randomized Clinical Trials Assessing Blood Loss during Major Surgery**

	HES 130/0.4 vs. HES 200/0.5	P Value
Estimated blood loss	-404 (-689 to -119)	0.006
Calculated blood loss	-149 (-247 to -50)	0.003
Drainage loss	-271 (-474 to -70)	0.009
RBC transfusion	-137 (-231 to -43)	0.004

All values for losses and transfusion requirements are given as ml, mean (95% confidence interval) for the difference HES 130-HES 200.

Data source: Kozek-Langenecker *et al.*<sup>54</sup>

HES = hydroxyethyl starch; RBC = red blood cell.

were associated with larger perioperative blood loss (10%) as compared to albumin. All other clinical outcome variables were similar between groups.

Currently, only limited information on the use of potato-derived tetrastarch (HES 130/0.42) is available. In patients undergoing gynecological surgery, Sander *et al.*<sup>56</sup> compared 6% HES 130/0.42 with 6% HES 200/0.5. There was little difference between groups, and the decrease of hemoglobin, hematocrit, and platelets was within the range expected due to intraoperative or postoperative blood loss or hemodilution due to the infusion therapy. However, only small volumes were administered, and the power of the study was too small to detect significant differences between study groups.

The evidence base for waxy maize-derived HES (6% 130/0.4) is particularly strong; overall, there are more than 50 published studies reporting on the coagulation effects of waxy maize-derived HES 130/0.4, including more than 20 Phase II to IV studies. These studies confirm that, unlike earlier generation HES preparations, the tetrastarches have minimal effect on coagulation.

**Tetrastarches: Accumulation and Tissue Storage.** HES molecules with a higher *in vivo* MW resulting from increased MS tend to be stored in tissue before being metabolized by amylases. Due to the more rapid clearance of the latest generation of tetrastarches, it is expected that tissue accumulation and its clinical manifestations will not be observed with the same frequency as compared to older starches.

Numerous reports based on human biopsy can be found to indicate that early generation HES products accumulate in various tissues, including liver, skin, cutaneous nerves, and possibly the placenta.<sup>57-66</sup> Deposits can persist for prolonged periods, depending on the cells affected. These reports suggest that there is a dose-dependent pattern of deposition; at lower doses, HES deposits are detected in the histiocytes, whereas they appear at higher doses in keratinocytes, sweat gland epithelia, endothelial cells, and perineural, endoneurial, and Schwann cells in cutaneous nerves. Light and electron microscopy studies show deposits of HES within dermal macrophages and endothelial cells, and adjacent to nerve fibers.<sup>63</sup>

In a multiple-dosing study using radio-labeled HES solutions in rats, Leuschner *et al.*<sup>67</sup> noticed a significantly lower storage of 10% HES 130/0.4 compared to 10% HES 200/0.5. Fifty-two days after the last infusion, the remaining radioactivity of pentastarch in the total body was nearly four times higher than that of the tetrastarch. As a result of similarities in the study design, the authors were able to compare their results with those of Hulse and Yacobi,<sup>68</sup> who investigated the distribution and elimination of <sup>14</sup>C-labeled 6% HES 450/0.7 in rats. Both of the lower-MW HES products showed much lower tissue storage than the hetastarch studied by Hulse and Yacobi. In healthy volunteers, Waitzinger *et al.* demonstrated that 6% and 10% solutions of HES 130/0.4 showed no clinically relevant accumulation in plasma either after single doses or after repetitive infusion over 10 days.<sup>19,20</sup>

The main clinical manifestation of tissue storage is HES-related pruritus, which was first reported in otologic patients who had received relatively high repeated doses of HES.<sup>69</sup> The pruritus arises from long-term cutaneous storage of HES molecules, and it may last for months after exposure.<sup>58,70</sup> The incidence appears to be related to the MS and the cumulative infused dose,<sup>70-73</sup> and it is resistant to treatment by glucocorticoids, antihistamines, acetaminophen, and neuroleptic drugs.<sup>74</sup>

By comparison, Ellger *et al.* found no incidence of postoperative itching in any of the 40 patients undergoing elective urologic cancer surgery, although relatively high doses of waxy maize-derived HES 130/0.4 (6%) were given.<sup>51</sup> In other studies of HES 130/0.4 using relatively high doses, pruritus did not seem to be a clinical problem.<sup>50,52,75,76</sup>

Two investigations using high-dose HES 130/0.4 in patients with acute ischemic stroke reported a low incidence of pruritus. Using a 10% solution and a mean total infusion volume of over 5,000 ml, only 2 of 70 patients developed transient itching,<sup>77</sup> whereas only 3 patients out of 20 reported itching after total doses of 6,000 ml of a 6% solution.<sup>78</sup> The follow-up period in both trials was 90 days, which is a sufficiently long period of time for symptoms of HES-induced pruritus to emerge.

Recently, Klemm *et al.* reported the results of a randomized, double-blind study in patients with sudden hearing loss where patients received 15, 30, or 45 g/d HES 130/0.4 or 5% glucose over a period of 6 d.<sup>75</sup> In this study, there were no significant differences regarding adverse events, including pruritus, in any of the treatment groups or the group that received placebo. Of 208 patients analyzed, 2 patients experienced pruritus that was deemed to be related to the study drug. One of the patients experienced severe pruritus on the whole body but recovered without further treatment after HES infu-

sion was stopped. Overall, all skin and subcutaneous tissue adverse events were less frequent than those related to the primary diseases of the ear, nose, and throat.

Similarly, in a randomized study on 120 patients undergoing coronary artery bypass surgery, high doses of 6% HES 130/0.4 and 6% HES 200/0.5 did not contribute to pruritus.<sup>52</sup>

**Tetrastarches: Effects on Plasma Bilirubin.** Waxy maize-derived HES 130/0.4 has been extensively studied in a large number of clinical trials. None of these reports suggest that it is associated with deterioration of liver function compared to controls. One study with potato-derived HES (130/0.42) reported mild to moderate hyperbilirubinemia as a significant adverse event.<sup>56</sup> Sixty patients undergoing major gynecological surgery were randomized to receive either potato-derived 6% HES 130/0.42 or 6% HES 200/0.5 as needed depending on individual requirements to maintain hemodynamic stability until 6 h postoperatively up to a maximum daily dosage of 33 ml/kg. The most common adverse event was mild to moderate hyperbilirubinemia observed in 36 patients (17 pentastarch, 19 tetrastarch). The authors suggest that this has a questionable relationship to the study drug; postoperative hyperbilirubinemia may be induced by impaired excretion of bile and may be aggravated by increased bilirubin resulting from fragmented erythrocytes. However, similar findings have not been observed in any studies with waxy maize-derived HES. Furthermore, potato-derived HES 130/0.42 is the only tetrastarch to be absolutely contraindicated in patients with severe hepatic impairment.††

**Tetrastarches: Effects on Renal Function.** A number of earlier reports suggest that HES products may have adverse effects on renal function. However, more recent studies using third-generation products have not reported unfavorable effects, suggesting that the lower tendency of these products to accumulate may improve their profile with regard to renal function.

Concerns about the possible deleterious effects of HES on renal function were first raised by Legendre *et al.* in a retrospective study investigating the association between HES exposure of organ donors and the subsequent tissue storage in the recipients.<sup>79</sup> Cittanova *et al.*<sup>80</sup> later found a link between the use of HES 200/0.62 in kidney donors and the subsequent need for hemodialysis in the recipients, but Deman *et al.* could not confirm these results in their retrospective analysis.<sup>81</sup> The authors suggested that the nephrotoxicity noted by Legendre *et al.*<sup>79</sup> might have resulted from the use of a particular preservation agent. Other researchers also failed to find any deterioration in renal function associated with the use of various HES preparations: 6% HES 200/0.5 and HES 70/0.5,<sup>82</sup> 6% HES 200/0.5, 6% HES 200/0.62, and 6% HES 450/0.7,<sup>83</sup> even when high doses were used.<sup>50</sup>

†† SmPC Tetraspan 6%. Available at: [www.fachinfo.de](http://www.fachinfo.de). Accessed May 15, 2009.

The situation was further confused by two studies that suggested deterioration of renal function associated with certain HES products. Schortgen *et al.* found in a prospective study that the incidence of acute renal failure in patients with severe sepsis was higher in those receiving 6% HES 200/0.62 than those who were treated with gelatin.<sup>84</sup> However, there were some limitations associated with this study, *i.e.*, mean creatinine at baseline was outside the normal range in the HES group, suggesting a greater risk for the development of renal failure. The second study was by Winkelmayer *et al.*, who performed a retrospective analysis of coronary artery bypass surgery patients receiving hetastarch and noted a modest reduction in glomerular filtration rate.<sup>85</sup> Winkelmayer used HES 670/0.75, which is known to accumulate in plasma,<sup>13,15</sup> and did not measure renal function but assessed it using the Cockcroft-Gault formula.

However, in a randomized study of elderly patients undergoing cardiopulmonary bypass surgery, Boldt *et al.* found no difference in the levels of kidney-specific proteins between patients who received 6% HES 130/0.4 and those who received gelatin.<sup>86</sup> In another randomized study with similar patients, comparing the same HES agent with 5% albumin, Boldt *et al.* again found no difference in renal function between the two groups.<sup>87</sup>

An important large-scale observational study of the effects of HES administration on renal function was carried out by Sakr *et al.*<sup>88</sup> In a retrospective analysis of data of 3,147 critically ill patients included in the SOAP study (Sepsis Occurrence in Acutely Ill Patients), it was found that HES *per se* was not an independent risk factor for adverse effects on renal function in the 1,075 patients who received HES. Neither the use of HES nor the dose administered was associated with an increased risk of renal replacement therapy, even in the subgroup of patients with severe sepsis and septic shock ( $n = 822$ ). These patients were also at particular risk for renal dysfunction because of a high incidence of cardiovascular dysfunction and preexisting renal impairment. Unfortunately, the authors did not distinguish between the types of HES preparations used; however, they did acknowledge that the use of newer HES preparations with a lower tendency to accumulate may have contributed to the favorable results.

A recent contribution to the debate about HES and renal function is a study on patients with severe sepsis.<sup>89</sup> This prospective, open label, randomized study (Efficacy of Volume substitution and Insulin therapy in Severe SEpsis [VISEP] study) investigated the influence of a colloid (pentastarch, 10% 200/0.5, HemoheS<sup>®</sup>; B Braun) *versus* crystalloid-based volume resuscitation and an intensified *versus* a conventional insulin therapy on organ function and survival.

The authors reported that the use of pentastarch as administered in this study was associated with a higher rate of acute renal failure and renal replacement therapy

as compared to a modified Ringer's lactate solution (lactate 45 mmol/l). Although the study protocol specified a maximum HES dose of  $20 \text{ ml/kg}^{-1}/\text{d}^{-1}$ , over 38% of the patients in this group received significantly more than the maximum dose and were treated over a long period (up to 21 days). These results are therefore not surprising; it has previously been reported that 200-kDa pentastarches and hyperoncotic solutions impair renal function and should not be used repeatedly.<sup>90-93</sup>

Unfortunately, the authors presented only a comparison of the pooled colloid *versus* crystalloid arms and a comparison of the pooled intensified *versus* conventional insulin therapy arms. Results of the single arms of the study have not been reported. This is an important omission; there is a strong trend towards an interaction of the two study interventions regarding the development of renal function ( $P = 0.06$ ). Therefore, it is not known to what extent intensified insulin therapy contributed to the development of acute renal failure in the group receiving pentastarch.

In the considerable body of clinical data on the third-generation HES 130/0.4, there have been no reports of adverse effects on renal function over and above those seen in control groups in patients who are considered to be at particular risk, such as those with previous mild to severe renal dysfunction,<sup>94,95</sup> the elderly,<sup>96</sup> and those receiving high-dose therapy.<sup>50</sup> Fenger-Eriksen *et al.*<sup>96</sup> performed studies in the area and found that a colloid-based fluid regime (6% HES 130/0.4) may preserve renal function to a greater extent than crystalloids in patients undergoing spinal surgery. Similarly, Godet *et al.*<sup>97</sup> suggested that 6% HES 130/0.4 was as safe as gelatin (Plasmion<sup>®</sup>; Fresenius France Pharma, Sevres, France) in patients with prior renal dysfunction undergoing abdominal aortic surgery. Although baseline renal function was impaired in all patients (creatinine clearance [CrCl] less than 80 ml/min), no drug-related unfavorable effects on renal function were found using HES 130/0.4 compared to gelatin.

One of the criticisms directed against many earlier studies, is that the follow-up periods have been relatively short.<sup>95</sup> Fifty patients undergoing cardiac surgery were randomized to either 6% HES 130/0.4 or 5% human albumin given perioperatively until the second postoperative day. After a 60-d follow up, it was found that kidney function in patients receiving tetrastarch was as preserved as with albumin. Although concentrations of kidney-specific proteins increased after surgery in both groups, there was no difference between groups. None of the patients developed acute renal failure leading to renal replacement therapy, neither during hospital stay, nor in the follow-up period.

Three recently published studies confirm these findings. In a randomized study of 50 patients assigned to either a balanced regimen (6% HES 130/0.42 plus crystalloid solution) or a saline-based regimen (the MS of the

HES is not specified, plus saline) kidney integrity was less altered with the HES 130/0.42. Levels of glutathione transferase alpha and neutrophil gelatinase-associated lipocalin were raised in both groups, but less so in the group with the plasma-adapted solutions.<sup>98</sup>

Another recent publication reports preliminary results of an observational study of pediatric patients aged up to 12 yr undergoing various types of surgery while receiving 6% HES 130/0.42. This noncomparative study evaluated the perioperative use of HES 130/0.42 in 1,000 children, with a particular focus on cardiovascular stability, hemodilution, acid-base balance, renal function, blood coagulation, and hypersensitivity. Reports on the first 300 children have shown no serious effects on renal function.<sup>99</sup>

Finally, an observational study on patients resuscitated with a variety of agents aimed to assess the risk of renal adverse events associated with the use of hypooncotic colloids, artificial hyperoncotic colloids, hyperoncotic albumin, and crystalloids.<sup>100</sup> The results confirm that hyperoncotic colloids are not indicated in renally impaired patients and may even be harmful.

In summary, the published data on this topic suggest that there are differences between the older and newer generations of HES and that the reports of adverse effects on renal function should not be extrapolated to newer HES products. Nine clinical trials on renal function demonstrate the safety of waxy maize-derived HES 130/0.4, and two recently published trials confirm that potato-derived HES 130/0.42 has no adverse effects on renal function.

**Tetrastarches: Special Patient Groups.** Extra caution is always needed when treating high-risk groups, such as the elderly, children, and those with renal impairment. Due to a higher incidence of comorbidities and changes in lung, kidney and cardiovascular function, the elderly are at increased risk for impairment of renal function. The waxy maize-derived tetrastarch HES 130/0.4 has been thoroughly studied in these groups and has a well-documented safety profile. In the elderly, HES 130/0.4 has been studied in patients undergoing abdominal surgery,<sup>82,101,102</sup> where it was found to be an adequate replacement for albumin<sup>102</sup> or gelatin.<sup>82</sup> In cardiac surgery patients, HES 130/0.4 was deemed to be as safe as gelatin,<sup>103</sup> offering a more persistent volume effect<sup>104</sup> and a lower risk of anaphylactoid reaction.<sup>105</sup>

Further studies on HES 130/0.4 have also confirmed its safety in surgery, where patients are at high risk for renal dysfunction<sup>94</sup>: abdominal aortic surgery,<sup>97</sup> spinal fusion surgery,<sup>106</sup> and surgery for aortic aneurysm.<sup>107</sup>

Waxy maize-derived HES 130/0.4 is the only third generation HES with controlled clinical data in children. In this context, Standl *et al.* reported that waxy maize-derived 6% HES 130/0.4 was as safe and well tolerated as albumin when used in pediatric surgery.<sup>108</sup> Other studies reached similar conclusions when using 6% HES 130/

0.4 and 4% albumin in pediatric cardiac surgery<sup>109,110</sup> and spinal fusion,<sup>106</sup> whereas Sümpelmann *et al.*<sup>99</sup> report a very low level of adverse reactions with potato-derived HES 130/0.42 in a noncomparative observational study in children.

**Tetrastarches: Effects on Microcirculation and Oxygenation.** There is increasing evidence that some plasma substitutes possess additional properties that have beneficial effects on organ perfusion, microcirculation, tissue oxygenation, inflammation, endothelial activation, capillary leakage, and tissue edema over and above their volume replacement effects.

Hypovolemia may initiate a cascade of pathophysiological processes, such as stimulation of the sympathoadrenergic and renin-angiotensin systems that may result in inadequate tissue perfusion and decreased oxygen supply to the tissues. Ideally, therefore, fluid therapy should confer beneficial effects on microcirculation and tissue oxygenation.

Third generation HES 130/0.4 has positive effects on tissue oxygenation and microcirculation in patients undergoing major abdominal surgery.<sup>111</sup> Intravascular volume replacement with a 6% solution improved tissue oxygenation compared with a crystalloid-based volume replacement strategy using lactated Ringer's titrated to similar hemodynamic endpoints. The tetrastarch was also found to produce a greater and earlier increase of tissue oxygen tension as compared to two pentastarch solutions (6% HES 70/0.5 and 6% HES 200/0.5) when administered to volunteers and a more pronounced and earlier increase of skeletal muscle oxygen tension.<sup>112</sup>

Lang *et al.* attribute these beneficial effects of tetrastarches to improved microperfusion and reduced endothelial swelling; crystalloids mostly distribute in the interstitium, causing endothelial tissue swelling and reduced capillary perfusion.<sup>111</sup> Neff *et al.*<sup>113</sup> suggest that HES with lower MS may decrease erythrocyte aggregation, thereby reducing low-shear viscosity of the blood. However, more studies are needed to investigate this issue more thoroughly.

**Tetrastarches: Effects on Systemic Inflammation and Endothelial Activation.** As with all forms of trauma, surgery triggers a systemic inflammatory response with the release of inflammatory mediators into the systemic circulation. Proinflammatory cytokines, such as interleukin-6 (IL-6) and IL-8, play an important role in regulating the acute inflammatory phase. Cell adhesion molecules, such as E-selectin, endothelial leukocyte adhesion molecule-1 (ELAM-1), and intercellular adhesion molecule-1 (ICAM-1), regulate the interaction of immune cells with each other, the endothelium, and the extracellular matrix. It has been demonstrated that release of IL-6 correlates with the severity of surgery,<sup>114</sup> whereas large increases in circulating adhesion molecules have been found in patients with severe sepsis.<sup>115</sup> In particular, surgery of the intestine is associated with a

greater inflammatory response than other types of surgery,<sup>116</sup> and the elderly population may also show an enhanced inflammatory response.<sup>117,118</sup> It is, therefore, of interest to assess the effects of volume replacement solutions on the mediators of inflammation.

In a study of patients undergoing abdominal surgery, Lang *et al.*<sup>119</sup> found a significantly lower increase of the proinflammatory cytokines IL-6 and IL-8 in patients receiving 6% HES 130/0.4 compared to those receiving lactated Ringer's solution. There were also significantly lower serum concentrations of soluble ICAM-1 (sICAM-1) in the HES group.

Likewise, in patients undergoing major abdominal surgery, Boldt *et al.*<sup>102</sup> reported a similar attenuation of plasma levels of IL-6 in patients receiving 6% HES 130/0.4 compared to those receiving 5% albumin. Plasma levels of endothelial adhesion molecules (sELAM-1, sICAM-1) were also significantly lower in the HES group, returning to normal on the day after surgery and remaining elevated in patients receiving albumin. In a study of elderly patients undergoing cardiac surgery, inflammatory response was similar in groups receiving 5% albumin and those receiving 6% HES 130/0.4, whereas endothelial activation was lower in the HES group.<sup>87</sup> Boldt speculates that the beneficial effect of HES 130/0.4 on inflammation and endothelial activation may be the result of some direct, substance-specific effects on endothelial cells resulting in reduced release of adhesion molecules.<sup>102</sup> Using endothelial cell cultures, Collis *et al.*<sup>120</sup> found that lipopolysaccharide-stimulated expression of adhesion ligand P-selectin was inhibited by HES.

Volta *et al.*<sup>121</sup> reported that HES 130/0.4 was able to selectively inhibit the activity of matrix metalloproteinase-9 (MMP-9) *in vitro* compared to lactated Ringer's solution. This was confirmed in 36 patients scheduled for colon cancer surgery who were randomized to 6% HES 130/0.4, 3.4% polygeline or lactated Ringer's solution. After surgery, plasma levels of MMP-9 and tissue inhibitor of MMP-9 (TIMP-9) were higher in all three groups, but they were significantly lower in the tetra-starch group than in the other two groups.

A number of *in vitro* and animal studies shed light on the possible mechanisms by which HES might affect the inflammatory process. Using cultured human microvascular endothelial cells and mice, Dieterich *et al.*<sup>122</sup> found that physiologically relevant concentrations of tetra-starch were able to reduce neutrophil adhesion *in vitro*, while vascular leakage, and pulmonary edema induced by hypoxia exposure were reduced in animals treated with HES. Nohé *et al.*<sup>123</sup> studied the expression of adhesion molecules on native and cytokine-activated endothelium from umbilical veins after pretreatment with gelatin and various preparations of dextran and HES. The authors concluded that synthetic colloids inhibit neutrophil adhesion by a neutrophil-dependent

mechanism rather than interfering with endothelial cell activation.

## Carrier Solutions

Although most published studies focus on the effect of HES, some clinicians have recently questioned whether the type of solvent used may also have a significant effect on hemodynamics and organ function. The two types of solution in current use are 0.9% saline and "balanced" solutions that aim to mimic the biochemical composition of human plasma. Although the exact composition of so-called balanced solutions varies, they generally have fewer sodium and chloride ions than saline, but contain potassium and bivalent cations, and metabolizable anions, such as acetate, malate, or lactate.

### *Hyperchloremic Metabolic Acidosis*

Normal saline (NaCl 0.9%) contains around 154 mmol/l of sodium and chloride ions. Importantly, there is concern that infusion of high volumes of normal saline may lead to the development of hyperchloremic metabolic acidosis, due to the high chloride load rather than to dilution of bicarbonate.<sup>124</sup> This has been suggested by a number of reports<sup>125-127</sup> in which the development of hyperchloremic metabolic acidosis has been noticed in patients receiving large quantities of sodium and chloride in the infusion solution. However, it seems that it typically occurs only after the infusion of more than 3 l of normal saline; for patients receiving 2 l or less of a normal saline solution, there is only modest or no change in base excess. With respect to the use of colloids, patients rarely exceed this limit, even in high-blood loss surgery. Typical values for total volume infused until the end of surgery reported in the literature for cardiac, orthopedic, and abdominal surgery range from 1,220 to less than 2,000 ml.<sup>30,31,103,111,128-130</sup> One study of colonic surgery reported total volumes of 2,700 ml,<sup>121</sup> and two studies of abdominal surgery reported values of 2,110<sup>101</sup> and 3,533 ml, respectively.<sup>102</sup>

Although disturbance of the acid-base balance can certainly be observed in patients receiving high volumes of saline, its clinical relevance is unclear.<sup>126,127</sup> Some researchers suggest that it is benign and self-limiting.<sup>126,127,131</sup> Others are convinced that it may impair renal and splanchnic perfusion as indicated by reduced urine flow, abdominal discomfort,<sup>132</sup> or impaired gastric mucosal perfusion.<sup>125</sup> It has also been suggested that it may interfere with the shift of electrolytes across cellular membranes.<sup>133</sup> Unfortunately, there are no large-scale studies dealing with this issue that can be considered truly evidence-based.

It has been suggested that balanced solutions may be more beneficial in terms of blood coagulation and platelet function.<sup>134,135</sup> In these two *in vitro* studies, the

authors compared the effects of potato-derived tetra starch HES 130/0.42 in a balanced solution (Tetraspan<sup>®</sup>; B Braun), waxy maize-derived starch HES 130/0.4 in a saline carrier (Voluven<sup>®</sup>), and Ringer's lactate. Activated partial thromboplastin time, Factor VIII clotting activity, von Willebrand factor, and platelet function were measured in 48 healthy individuals,<sup>134</sup> and effects on hemostasis were measured in 10 volunteers by using rotation thrombelastography and whole blood aggregometry.<sup>135</sup> The results suggest that HES 130/0.42 in a balanced solution had fewer negative effects on coagulation.<sup>134,135</sup> In the latter study, a comparison of the values obtained at varying degrees of dilution suggest that the effects can be attributed to a dilutional effect rather than to a substance-specific effect. However, the authors acknowledge that it is difficult to translate *in vitro* findings into the clinical setting. The *in vivo* coagulation system is very complex, and *in vitro* studies cannot take into account a number of factors that are present in the circulation: the role of the endothelium and surgery-related effects – such as hypercoagulability – cannot be modeled. In addition, in the clinical setting, HES is usually given with large amounts of crystalloids, and the effects of metabolism and excretion are not included in the *in vitro* setting. Furthermore, in the *in vitro* situation, calcium content of the diluent solution is critical and will determine the calcium available for the coagulation process, whereas plasma calcium concentrations *in vivo* are well maintained from sources such as bone.

A small number of studies are available comparing balanced and unbalanced solutions. Boldt *et al.* enrolled 30 patients scheduled for major abdominal surgery into a study where they were randomized to receive the potato-derived tetra starch, 6% HES 130/0.42 in either a balanced solution (Tetraspan<sup>®</sup>) or in saline (Venofundin<sup>®</sup>).<sup>136</sup> Concomitant crystalloids in the two groups were also either balanced or saline-based, respectively, and were given in a 1:1 ratio with the associated colloid. The two groups showed no difference in terms of hemodynamics, coagulation measures or kidney function, but the mean base excess was significantly more negative in the group receiving the saline-based fluids.

More recently, in a comparative study with elderly cardiac surgery patients, Boldt *et al.* found that the inflammatory response and endothelial activation were lower in patients receiving a balanced regime of HES 130/0.42 plus crystalloid, compared to those receiving a saline-based regime. However, the saline HES type was not completely specified.<sup>98</sup>

In a study involving 81 patients undergoing elective valve surgery or coronary artery bypass grafting,<sup>137</sup> the waxy maize-derived tetra starch HES 130/0.4 was compared in two forms, either in a saline solution (Voluven<sup>®</sup>) or in a balanced solution (Volulyte<sup>®</sup>). This study did not include the confounding factor of using different

concomitant crystalloids. Rather, both patient groups received Ringer's solution as a perioperative crystalloid. Again, there was a significant difference in hyperchloremia, which was lower in the Volulyte<sup>®</sup> group. However, safety was equivalent apart from the markers of acid-base status, and outcome variables were not different between groups. The authors concluded that it is probably unnecessary to use balanced solutions if only moderate infusions are required, whereas balanced colloids can be used to reduce chloride load when large volumes are required.

## Conclusion

Laboratory, animal, and clinical studies all demonstrated that there are clear physicochemical and pharmacokinetic differences between the generations of HES, mainly resulting from modifications to the MS and the pattern of substitution. Both of these result in differences in the *in vivo* MW as well as plasma and tissue persistence. Apparently small variations in MS have significant effects on the coagulation system and renal function. Notably, the third generation of tetra starches shows a significantly improved safety profile without any loss of volume effect compared to first- and second-generation HES preparations. Variation in the source material for HES also produces measurable pharmacokinetic differences in the end product. This review of the available clinical data demonstrates that HES should not be regarded as one homogenous group, and data for one product should not be extrapolated to another.

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