INFLUENCE OF CARDIAC OUTPUT, INJECTION TIME AND INJECTION VOLUME ON THE INITIAL MIXING OF DRUGS WITH VENOUS BLOOD AFTER I.V. BOLUS ADMINISTRATION TO SHEEP

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SUMMARY

The aim of this study was to quantitate factors affecting the initial "peak" of the pulmonary artery (PA) drug concentrations after i.v. bolus drug administration, which is a determinant of the subsequent drug uptake into both the lungs and other well-perfused organs. Indocyanine green (ICG) was used as a marker drug in anaesthetized (1.5% halothane) sheep prepared with an inferior vena cava injection catheter and a large-gauge pulmonary artery blood sampling catheter. For three ranges of cardiac output, 2.5-mg doses of ICG were injected in the following combinations: 10 ml injected over 1, 5 or 10 s; 5 or 25 ml injected over 1 s. On-line PA ICG concentrations were recorded for approximately 60 s using a densitometer. The mean maximum PA ICG concentrations (2–8 mg litre−1), the mean times at which they occurred (7–18 s after injection) and the time lags before ICG was detected in the PA (4–9 s), were inversely related to cardiac output, but linearly related to the time over which the injection was made. The area under the curve of the peak was related inversely to cardiac output only, while the aspect ratio of the peak was related inversely to the time over which the injection was made only. The injectate volume had no effect on any of the measured values. We conclude that, in some circumstances, the rate of injection of drugs with narrow margins of safety should be tailored to the cardiac output of an individual.

KEY WORDS

Pharmacokinetics: bolus administration, peak pulmonary artery constriction.

Following rapid i.v. administration of a drug, the bolus of injected drug mixes with venous blood, travels along the venous vasculature to the right heart and is subject to first pass effects through the lungs and distributed to the remaining organs of the body according to their relative perfusion [1, 2]. An understanding of the determinants of the magnitude of the initial effects of drugs with narrow margins of safety, such as i.v. and local anaesthetics, requires a knowledge of the time-courses of the initial concentration of these drugs in well-perfused organs such as the heart and brain. It is apparent that the magnitude of these initial effects and organ drug concentrations are influenced to some extent by each step in the chain of events occurring as part of the initial passage of the bolus of drug.

These issues were well recognized by Crawford [1] and other earlier workers, who advanced the concept of a drug administered as an i.v. bolus entering the blood stream as a "slug" which travelled for two to three circulations before uniform dispersion in the blood. The large initial concentrations of drug in the slug were thought to be a cause of the transient haemodynamic effects of drugs such as opioids, barbiturates and phenothiazine derivatives after rapid bolus administration. Although Crawford foresaw the need for extensive studies of the blood and tissue concentrations of drugs and their effects after bolus administration, and of the influence of physiological factors such as increased shunting on these processes, only a limited number of such studies has appeared in the literature.

One of the few experimental methods for determining the serial tissue concentrations of drugs in vivo while simultaneously measuring the effects of the drug [3] is the application of mass balance principles [4] to individual organs such as the heart [5, 6]. However, despite the importance of the first pass of a drug through the lungs [7], it has not been possible to study the uptake and elution of drugs in the lungs using mass balance principles because the time-course of the initial drug concentrations in pulmonary artery blood entering the lungs changes too rapidly to characterize with conventional blood sampling methods [8]. We have shown that these are limited to a sampling interval of approximately 4 s and that more rapid sampling using the fraction collection technique may not be accurate [8].

This paper examines an alternative method of characterizing the initial peak drug concentrations in the PA following an i.v. bolus. Indocyanine green (ICG) was used as a marker drug which has the advantage that its concentration in whole blood can be measured continuously using a densitometer, and it is confined to the intravascular space. It is

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unlikely that the physicochemical properties of a drug would have any influence on the initial mixing process in venous blood, provided that all concentrations achieved were less than the solubility limit of the drug in blood. The method is essentially a modification of the dye dilution method for measuring cardiac output using vasculature indicators [9]. Thus, when considering the influence of various factors on the shape of the pulmonary artery drug peak, the Stewart–Hamilton equation [9] suggests a direct effect of cardiac output on the area of the peak entering the lungs. The effect of injection rate and volume on the shape of this peak is also of interest because these can be altered in the clinical setting.

If it is possible to identify the major factors affecting the shape of this peak, it should be possible to construct a simple equation that can predict the size and shape of the drug peak entering the lungs after i.v. bolus drug administration to sheep, thereby allowing studies of lung drug uptake and elution in the sheep preparation. The aim of this study was therefore to examine effects of cardiac output, injection rate and injection volume on the size and shape of the first “peak” in drug concentration in the pulmonary artery after i.v. bolus drug administration. An additional aim of more direct clinical relevance was to undertake a more formal and general analysis of the proposition of Scott [2] that the rate of injection of drugs greatly influences their toxicity.

METHODS

Sheep preparation

The studies were approved by the local Institutional Animal Ethics Committee. Four adult female sheep (weight 40–50 kg) were anaesthetized by induction with thiopentone 20 mg kg\(^{-1}\) and maintenance with 1.5 % halothane in 40 % oxygen, balance nitrogen. A 7-French gauge catheter for ICG injection was placed via the jugular vein with its tip in the inferior vena cava distal to the confluence of the renal veins. A 5-cm long, 9-French gauge, thin-walled pulmonary artery catheter was placed directly in a pulmonary artery via a thoracotomy. The shortest catheter possible was used, to minimize the dispersion of the ICG peak within the catheter reported previously [8]. A thermistor-tipped pulmonary artery catheter (Swan–Ganz, Edwards Laboratories, Irvine, CA, U.S.A.) was placed in the pulmonary artery via the jugular vein for cardiac output measurement, with a separate 7-French gauge right atrial catheter for injection of the cold indicator.

Cardiac output measurement

Cardiac output was measured using the thermodilution method and the thermistor tipped catheter with injections of 10 ml of ice-cold 5 % glucose. Cardiac output at a given time was taken as the mean output determined from three consecutive injections. Three distinct ranges of cardiac output were achieved consecutively in each sheep. The “medium” range was the cardiac output of the sheep when stable anaesthesia was obtained with 1.5 % halothane. The “low” range was the cardiac output when stable anaesthesia was obtained with 4–5 % halothane. The “high” range was the cardiac output during anaesthesia with 1.5 % halothane with a concomitant i.v. infusion of isoprenaline (titrated against cardiac output, infusion rate 0.5–3 \(\mu\)g min\(^{-1}\)).

ICG administration and measurement

ICG (Cardio Green, Hyson, Westcott and Dunning Inc., Baltimore, U.S.A.) was injected via the inferior vena cava catheter using a contrast media injector for angiography (Angiomat 3000, Viamont Hobbs, Barber–Colman Company, Rockford, Illinois, U.S.A.). Three separate 2.5-mg doses of ICG were injected for each of the following combinations of injection volume and time: 10 ml injected over 1, 5 and 10 s for the low, medium and high ranges of cardiac output; 5 and 25 ml injected over 1 s for the medium cardiac output. ICG solutions were prepared freshly on each experimental day, and were diluted with 0.9 % saline.

Immediately before each injection, cardiac output was determined as described previously. During and after each injection, ICG concentration in the pulmonary artery was recorded continuously using a densitometer as described below. The densitometer (Model DC-410, Waters Instruments Inc., Rochester, MN, U.S.A.) was connected directly to the end of the PA catheter. An extension tube then connected the densitometer to a 50-ml syringe in a withdrawal pump (Series 900, Harvard Apparatus, Millis, MA, U.S.A.) that could withdraw blood through the catheter at a constant rate of 15 ml min\(^{-1}\). After each period of measurement, the blood in the syringe was reinfused into the sheep before the next measurement, and the zero of the densitometer reset. The output of the densitometer was amplified (Model TD-1A, Waters Instruments Inc., Rochester, MN, U.S.A.) and recorded on a chart recorder (Model B31-1H, Rikadenki Kogyo Ltd, Tokyo, Japan). The densitometer was calibrated using a two-point calibration with blank blood taken from the sheep before each study and spiked to ICG concentrations of 0 and 10 mg litre\(^{-1}\).

Data analysis

The injection rate was expressed as the time over which the injection was made (\(t_{\text{inj}}\)), which simplified data analysis. The following attributes of each peak were measured (fig. 1) and calculated as the mean of the three measurements made for each combination of cardiac output, injection time and injection volume. The lag time (\(t_{\text{lag}}\)) was designated the time between injection of ICG and first appearance in pulmonary artery blood. The maximum ICG concentration (Cmax), and the time of the maximum concentration after injection (tCmax) were also recorded. Peak area (AUC) was determined using both the triangulation method used for cardiac output determinations [9] and the cut and weigh method (with linear extrapolation of the downslope of the curve). The peak aspect ratio was calculated as the ratio of peak height and the peak width at half peak height. Thus a high aspect ratio shows that the
peak was “tall and thin”, while a low ratio shows
that the peak was “short and fat”.

Multiple linear regression was used to produce
multiple linear equations describing the relationship
of each attribute of the peak (e.g. t\text{max}, C\text{max})
with the variables cardiac output, injection time and
injection volume and their inverses. The use of the inverse
is obvious for attributes such as AUC which would
be expected to be related inversely to cardiac output,
but was examined for all variables as it was not
possible to predict from first principles if, for
example, an attribute such as peak aspect would
be linearly or inversely related to injection volume.
If the coefficients of a variable were not statistically
significantly related to injection volume, suggesting that
greater cardiac outputs were associated with a greater mean flow
velocity between the injection site and the pulmonary
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Three comparable and statistically different ranges
of cardiac output were achieved in each sheep. The
combined mean low, medium and high ranges were
2.49 (sd 0.34), 4.59 (0.36) and 8.25 (1.57) litre min\(^{-1}\),
respectively for all sheep. Typically, for large cardiac
outputs and short injection times, the peaks were of
high aspect and had the classical indicator dilution peak shape (fig. 1). For long injection times and
small cardiac outputs, the peaks were of low aspect
and appeared to approach a steady-state concentration
during the injection (fig. 1). For the smallest cardiac output and the briefest injection time, there
appeared to be a maximum peak aspect that could be
achieved using this experimental system. Decreasing
the injection time to 0.25 s to simulate instantaneous
injection produced peaks essentially identical to
those for the 1-s injection times. Thus it would
appear that achieving a higher aspect ratio peak was
not possible within the hydrodynamic constraints of
the experimental system used. As stated previously,
these points were not used in the regression analysis.
Recirculation had only minor effects on the down-
slope of the peak in comparison with the use of ICG
dye for cardiac output measurements (which usually
uses arterial blood).

The regression coefficients (R\text{2}) ranged from 0.909
to 0.970, showing good linear relationships (table I). Altering injectate volume had no statistically sig-
nificant effect on any of the variables measured, and
is therefore not included in the following analysis.
The peak lag (t\text{max}) ranged between approximately
9 and 15 s and, as expected, was related inversely
to cardiac output, suggesting that greater cardiac
outputs were associated with a greater mean flow
velocity between the injection site and the pulmonary

\text{RESULTS}

\begin{table}[ht]
\begin{center}
\begin{tabular}{l c}
\hline
\textbf{Attribute} & \textbf{Equation} \\
\hline
\text{Cmax} & \text{Cmax} (\text{mg litre}^{-1}) = 5.78 \pm 1.16 / \text{CO} - 0.58 \times t_{\text{lnJ}} \\
& \text{R}^2 = 0.947. \\
\text{Cmax} & \text{SE of the coefficient: 0.60, 2.11 and 0.066, respectively.} \\
& \text{Area} (\text{mg litre}^{-1} \text{s}) = 124 / \text{CO} \\
& \text{Cmax (s)} = 3.27 \pm 1.57 / \text{CO} + 0.781 \times t_{\text{lnJ}} \\
& \text{SE of the coefficients: 0.95, 2.97 and 0.093, respectively.} \\
& \text{R}^2 = 0.970. \\
\text{R}^2 & \text{2.61} / t_{\text{lnJ}} \\
& \text{SE of the coefficients: 0.19.} \\
\text{R}^2 & \text{0.970.} \\
\hline
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Fig. 1. Left: An example of a high aspect indocyanine green peak
in the pulmonary artery. Right: An example of a low aspect
indocyanine green peak in the pulmonary artery. The various
attributes of the peak that were measured are also indicated.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Time of maximum indocyanine green (ICG) concentration
in the pulmonary artery (Cmax) against cardiac output (CO).
Injections of ICG 2.5 mg were made over 1 s (O), 5 s (V) or 10 s
(□) into the inferior vena cava for the low, medium and high
cardiac output groups. Data are mean values; error bars represent
SD of the time of peak maximum (vertical error bars) or cardiac
output (horizontal error bars) for the three injections in each of
four different sheep represented by each symbol.}
\end{figure}
artery. tCmax was statistically related to the time taken for injection, but the effect was small (table I).

The relationships for the remaining variables are shown in figures 2–5. Note that an inverse relationship between the variables and cardiac output produces hyperbolic curves on these plots. tCmax was between approximately 7 and 18 s (fig. 2). Longer injection times were associated with delays in tCmax and there was an inverse relationship between tCmax and cardiac output (table I). Mean Cmax was between approximately 2 and 8 mg litre⁻¹. Longer injection times were associated with linear decreases in Cmax and, again, there was an inverse relationship between Cmax and cardiac output (table I, fig. 3).

There was no statistical difference between the area measurements made using the two methods, and all results were calculated from those obtained using the “cut and weigh” method. In contrast to Cmax, the peak area was independent of injection time and was inversely related to the thermodilution cardiac output (table I, fig. 4). Conversely, the peak aspect was inversely proportional to the time taken for the injection only (table I, fig. 5).

DISCUSSION

The characteristics of the initial mixing and lung uptake of drugs after bolus administration is of particular importance for drugs that act rapidly and have a narrow margin of safety, such as thiopentone [10] and local anaesthetics [2]. However, there appear to be two major experimental approaches to studying this problem. One approach seeks to describe this initial period in terms of compartmental modelling [10,11]. Initial deficiencies in this area [12] have been overcome by more frequent blood sampling and concurrent administration of an intravascular indicator [10,11], but all methods are hampered by their unrealistic requirement to represent the blood volume as one (occasionally two) well-mixed compartments. The second approach embraces the concepts of Crawford [1]. Rather than requiring...
Instantaneous mixing of drug with the blood pool, a more physiological description of the movement of an injected drug along the vasculature is used. This generally requires measurements of drug concentrations entering or leaving (or both) organs such as the lungs [13, 14], heart and brain. The advantage of this approach is that the influence of haemodynamic and other factors on the passage of the drug is readily determined.

In contrast with studies of steady-state, or near steady-state, drug uptake into the lungs [15], the studies in this paper address the situation of very rapid and very transient drug uptake into the lungs. Indeed, it has been shown that the passage of drugs through the lungs in this situation is analogous to the passage of a drug through a chromatography column [16]. While some drugs are retained significantly by the lungs before their appearance in arterial blood, others pass rapidly through the lungs at a speed determined by the blood flow through the lungs. In each case, interpreting the behaviour of the drug in the lungs requires a knowledge of the time course of drug concentrations entering and leaving the lungs. While the latter, the initial time course of the arterial drug concentrations, can be characterized by methods of rapid blood sampling [6], the former changes too rapidly for this approach. Although the double indicator method provides one way of examining the lung uptake of drugs from arterial concentrations alone [13, 14], the present studies are part of an alternative method of studying drug uptake, which has the advantage of identifying the factors influencing the attributes of the drug peak entering the lungs.

The data agree qualitatively with the predictions of indicator dilution theory, the observations of Crankshaw on the effect of injection rate on the initial arterial concentrations of thiopentone [17] and the proposition of Scott [2]. The data showed that the volume of an i.v. bolus has no effects on the attributes of the initial drug peak entering the lungs. This is not surprising, considering the substantial mixing which occurs when a drug is injected into the blood and in the chambers of the right heart, and supports the notion of Crawford [1] that “the only good reason for diluting a drug prior to injection (other than minimising the possibility of local tissue injury) is that by so doing, the rate of injection tends to be diminished”.

By the Stewart–Hamilton equation, the inverse of the peak area should be proportional to cardiac output, and this was confirmed by the regression analysis of AUC and cardiac output (table I) demonstrating internal consistency in the experimental system. However, when it was attempted to find a description of the shape of these curves with respect to injection time and cardiac output, it was apparent that classical indicator dilution theory [18, 19] was constrained to producing curves of the type shown in figure 1 (left), and is not able to describe the shape of curves obtained for slower injections and smaller cardiac outputs. In these cases, the peaks were of the form shown in figure 1 (right), with the ICG concentration increasing to a steady state. From steady-state indicator dilution theory [20], it is possible to calculate that the concentration in the pulmonary artery at this point (Cmax) is described by the following equation:

\[ C_{\text{max}} = \frac{D}{t_{\text{inj}} \cdot CO} \]  

where \( D \) = total dose injected; \( t_{\text{inj}} \) = time over which the dose was injected; \( CO \) = cardiac output. For shorter injection times and greater cardiac outputs, it is apparent that the peak does not have time to reach this value and the shape of the peak is a factor of the extent of dispersion during vascular transit. There appears to be no unifying theory able to describe the shape of both types of peaks in terms of easily measurable variables.

As an alternative, multiple linear regression was used to produce multiple linear equations describing the relationship of each attribute of the peak (e.g. Cmax, PA drug concentrations) with cardiac output, injection time and injection volume or their inverses. The final equations showed good linear relationships (table I). A principal use of these regression data is of a quantitative nature for characterizing drug uptake into the lungs. Thus they can be used to interpret the time course of arterial drug concentrations leaving the lungs after i.v. bolus administration with respect to the expected time course and characteristics of the PA drug concentrations. However, the proviso is made that they can only be used within the ranges examined experimentally (table I) and are of quantitative use only in a sheep preparation. In summary, it is concluded that a knowledge of cardiac output and the time over which a drug injection is made is sufficient to calculate the basic properties of the initial drug peak entering the lungs of sheep following i.v. bolus drug administration.

These data do have an important clinical message, however. The basic anatomical structure, size, distances and blood flow rates for the venous vasculature of sheep are similar to those for man. Furthermore, although drugs can be injected into peripheral veins in clinical practice, rather than the vena cava used in these studies, the additional transit times required for peripheral blood to enter the vena cava would not greatly influence the qualitative interaction between initial drug concentrations, injection time and cardiac output observed in these studies. Therefore, an important qualitative aspect of these data is to demonstrate the large influence of cardiac output, injection time, or both, on the time course of the initial blood concentrations of a drug. It was shown that the peak lag varied from approximately 4–9 s, reflecting the differences in linear velocity in the venous vasculature with changes in blood flow. Similarly, the value of \( r_{\text{Cmax}} \) was approximately 7-18 s. The contribution of this temporal variation is probably of minor importance in the clinical setting, but is of a magnitude similar to or greater than the delay in a drug peak caused by passage through the lungs [13, 14, 16]. Of more relevance were the changes in Cmax and AUC — these were both inversely related to cardiac output, but only Cmax was also related to the injection time. By manipulating both injection time and cardiac output, these factors could be adjusted to optimize the duration and extent of drug effect.
output, it was possible to vary both $C_{\text{max}}$ and AUC by a factor of approximately 4. In agreement with the conclusions of Crawford [1] and Crankshaw, Rosler and Ware [17], for drugs that have little uptake by the lungs, such a 4-fold variation in concentration of the initial "slug" of drug reaching vital organs may produce substantial differences in the initial effects of the drug. Furthermore, the peak aspect varied from 0.25 to 3, giving an almost 12 times variation. We are continuing to investigate which attributes of the initial drug peak ($C_{\text{max}}$, AUC or aspect) is more important in determining the rate and extent of drug uptake into organs such as the heart and brain, and the time course of drug effects.

Although the need to inject drugs with narrow margins of safety relatively slowly is well recognized in clinical practice, these data suggest patients with either very large or very small cardiac outputs may need special consideration. For drugs with narrow margins of safety that are not retained by the lungs, these patients may benefit from a more formal tailoring of i.v. bolus drug injection rate to their cardiac output. This will be resolved with further studies of the relationships between the uptake and elution of drugs in the lungs, heart and brain and the magnitude of their pharmacological effects.

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