Drug absorption from the small intestine in immediate postoperative patients

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Background. The effects of surgery on gastric emptying have been documented for a considerable time, but less is known about the effects in the small intestine. It is thought that there is minimal diminution in the absorptive capacity of the small intestine after operation, although there is no literature on drug absorption in the early period after surgery. This study investigated drug absorption from the small bowel in patients undergoing abdominal surgery.

Methods. A prospective study of patients undergoing major abdominal surgery in which patients acted as their own preoperative controls was carried out. Patients were administered the test substances, acetaminophen and 99mTcDTPA, before operation and 2 days after operation. Small intestine transit times, plasma concentrations and other pharmacokinetic variables were compared using Student’s paired t-test. Two complementary studies were carried out to establish pharmacokinetic parameters.

Results. There were no significant differences in the pre- and postoperative values of tmax, area under the curve, and area under the moment curve (AUMC) before and after operation (P>0.05). There were significant differences between the pre- and postoperative values of Cmax [Cmax (preop)>Cmax (postop); P<0.05] and the pre- and postoperative values of mean residence time (MRT) [MRT(preop)>MRT(postop); P<0.01].

Conclusions. Drug absorption from the small bowel in the postoperative patient does not differ significantly from its preoperative absorptive capacity.

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The gastrointestinal tract has significant alterations in its function after operation1–3 and this phenomenon has important implications for how soon after an operation a patient is able to resume feeding by the oral route, resume normal medications, and consequently how soon a patient can leave hospital after surgery.4,5 The effects of surgery on gastric emptying have been documented for a considerable time, but less is known about the effects in the small intestine. It is thought that there is minimal diminution in the absorptive capacity of the small intestine after operation.10–12 This is suggested by clinical experience with regimes for early postoperative feeding. The ad hoc practice of administering drugs via a nasogastric feeding tube reflects this with the presumption that drugs given in this fashion are absorbed normally. This may be more hope than reality.

The observation that permeability of the gut may be altered after operation13 and motility and hence mixing, are affected, as well as changes in splanchnic blood flow, all suggest that postoperative drug absorption may be impaired.14 Loss of intestinal integrity and changes in enterocyte morphology and composition occur after starvation.15–18 These changes are more often seen in critically ill patients13 who are part of the surgical case mix. These features may also influence enteral drug absorption.

This study investigated drug absorption from the small bowel in patients undergoing abdominal surgery.

Methods
Four substances were used to investigate small bowel absorption in patients after abdominal surgery: acetaminophen, 99mTcDTPA, gentamicin and indocyanine green. Acetaminophen is a lipophilic drug, a marker of transepithelial absorption and is also a marker for passive absorption
from the small bowel.\(^{19}\) Although acetaminophen has been widely used as a marker of gastric emptying,\(^{20–23}\) in this study it was chosen because of its rapid absorption by passive transport from the small bowel only. \(^{51}\)CrEDTA and \(^{113}\)mInDTPA are commonly used to measure transit times in the gut but have the disadvantage of long half-lives,\(^{24–28}\) precluding them from use in repeat studies over shorter intervals. Thus \(^{99m}\)TcDTPA, which has a much shorter half-life, was used mixed with acetaminophen syrup to measure gut transit times and secondarily, to study changes in membrane permeability. Indocyanine green was used as a marker of hepatic blood flow, thus indirectly giving information about gastrointestinal blood flow. Gentamicin was used to estimate the changes in the extracellular compartment as it is not bound to plasma proteins and the space it distributes into closely parallels the extracellular fluid compartment.\(^{29–30}\)

Three experiments were carried out: Study I the i.v. study, to determine the volume of distribution (\(V_d\), the hypothetical volume that relates the drug plasma concentration to the amount of drug in the body) and clearance of acetaminophen (\(C_L\), the volume of drug completely cleared of drug per unit time); Study II, the gastric study, to compare the maximum plasma concentration achieved (\(C_{\text{max}}\)) and the time taken to achieve that concentration (\(t_{\text{max}}\)) of acetaminophen before operation, as would happen under normal circumstances, and Study III, the intraduodenal study, to compare the bioavailability [area under the curve (AUC), \(C_{\text{max}}\) and \(t_{\text{max}}\)] of acetaminophen and \(^{99m}\)TcDTPA in the pre- and postoperative periods. All received Ethics Committee approval from the host institution.

The recruitment of patients was the same for all studies. Patients between the ages of 40 and 90 yr and were undergoing major abdominal surgery (e.g. resection of large bowel cancer or repair of an abdominal aortic aneurysm) were eligible. All those who were pregnant, had had previous gastrointestinal surgery, had diseases of the small bowel, for example Crohn’s disease, or were undergoing operations on the small intestine, were excluded. For all three studies, patients were studied on two separate occasions: 1–3 days before surgery, that is, when they were ‘normal’ and on day 2 after surgery.

The doses and reasons for using the individual study drugs are shown in Table 1. I.V. drug administration, was through the antecubital fossa in one arm and sampling was via the cannula in the contralateral arm.

### Drug administration

**Study I, the i.v. study**

0.1 g acetaminophen (1 g acetaminophen, 2 ml ethyl alcohol, 4 ml propylene glycol, water for injection to 20 ml; Dunedin Hospital Pharmacy Production Unit\(^{31}\)) was administered i.v. over 5 min immediately after gentamicin 80 mg [80 mg per 2 ml of gentamicin sulphate injection (DBL/Baxter) containing sodium methyl hydroxy benzoate, 4.12 mg and sodium propyl hydroxy benzoate 0.45 mg as preservative] was given i.v. over 5 min. The end of the acetaminophen injection was taken as \(t=0\).

**Study II, the oral study**

Acetaminophen syrup 1.5 g (30 ml Panadol\(^{\circledR}\) 250 mg ml\(^{-1}\)) was given orally followed by 30 ml of water. At the same time the patient was drinking the syrup, 80 mg gentamicin (supra vide) was given i.v. over 5 min.

**Study III, the intraduodenal study**

For the preoperative phase, a double lumen nasogastric/duodenal Mallinckrodt tube [Mallinckrodt No. 22107018, Mallinckrodt Laboratories, Athlone, Ireland (14 CH \(\times\) 120 cm), with adaptations\(^{\circledast}\) was placed under fluoroscopy in the second part of the duodenum. This was removed at the end of the second hour of the study. For the postoperative phase, the double lumen nasogastric/duodenal tube was placed manually in the second part of the duodenum whilst the abdomen was open. It remained in situ until after completion of the study or until the patient no longer needed it clinically.

On this occasion acetaminophen syrup 1.5 g (30 ml Panadol\(^{\circledR}\) 250 mg ml\(^{-1}\)) was mixed immediately before administration with \(^{99m}\)TcDTPA (Technelite™, Radiopharmaceutical Division, Du Pont Merck Pharmaceutical Co., Billerica, MA, USA, 1862) and administered via the nasoduodenal tube over a period of 5 min and followed by a 10 ml flush of water for injection and spigotting of the tube. At the same time, gentamicin (supra vide) and indocyanine green (0.5 mg kg\(^{-1}\) Cardio-Green\(^{\circledast}\), manufactured by Paesel+Lorei GMBH & Co., Frankfurt, Germany for Becton–Dickinson Microbiology Systems, Cockeysville, MD, USA) were administered i.v. over 5 min followed by a 3 ml flush of heparinized saline. The end of the

### Table 1 Drugs used, sources, route and times of administration, doses, and purposes for their use

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Time given</th>
<th>Duration of administration (min)</th>
<th>Reason for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Acetaminophen</td>
<td>1.0 g</td>
<td>I.V.</td>
<td>(t=0)</td>
<td>5</td>
<td>(V_d), clearance</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>80 mg</td>
<td>I.V.</td>
<td>(t=0)</td>
<td>5</td>
<td>Change in (V_d)</td>
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<td>1.5 g</td>
<td>Oral</td>
<td>(t=0)</td>
<td>5</td>
<td>(C_{\text{max}}, t_{\text{max}}, \text{AUC})</td>
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<tr>
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<td>Gentamicin</td>
<td>80 mg</td>
<td>I.V.</td>
<td>(t=0)</td>
<td>5</td>
<td>Change in (V_d)</td>
</tr>
<tr>
<td>III</td>
<td>Acetaminophen</td>
<td>1.5 g</td>
<td>Intraduodenal</td>
<td>(t=0)</td>
<td>5</td>
<td>Passive transcellular absorption, (C_{\text{max}}, t_{\text{max}}, \text{AUC})</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>80 mg</td>
<td>I.V.</td>
<td>(t=0)</td>
<td>5</td>
<td>Change in (V_d)</td>
</tr>
<tr>
<td></td>
<td>Indocyanine green</td>
<td>0.5 mg kg(^{-1})</td>
<td>I.V.</td>
<td>(t=0), (t=30)</td>
<td>5</td>
<td>Gut blood flow</td>
</tr>
<tr>
<td></td>
<td>(^{99m})TcDTPA</td>
<td>(\approx100) mBq</td>
<td>Intraduodenal</td>
<td>(t=0)</td>
<td>5</td>
<td>Passive paracellular absorption</td>
</tr>
</tbody>
</table>
acetaminophen injection was taken as \( t = 0 \). The indocyanine green dose was repeated at 30 min.

**Plasma/blood samples**

For each phase of each study, a blood sample (5 ml) was obtained immediately before administration of the investigational drugs and further samples were obtained at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180, 240 and 300 min. Before each sample was obtained, 2–3 ml of blood containing the heparin lock was drawn off and discarded into an empty container. The sample was then drawn, using a fresh syringe (5 ml) for each sample, and collected in 10 ml Becton–Dickinson heparinized Vacutainers, and assayed at a later time (see next section). Immediately after the sample was obtained, the line was flushed with 2–3 ml of heparinized saline. Exact timing of the samples ±10 s was noted. Blood was stored at room temperature until the end of the sampling period and then stored in a refrigerator at 4 °C until it was analysed for acetaminophen and gentamicin. The plasma was separated immediately before analysis.

**Gamma scintigraphy**

This was carried out only for the intraduodenal dosing study using a dual-headed Gamma Camera (Picker Prism 2000 with Odyssey Super Computer imaging system) with two 20° × 15° field of view detectors enabling single pass anterior and posterior views. Frames were taken at 5 min intervals over a 60 min period, starting from \( t = 0 \).

**Sample analysis**

Samples were split for analysis of acetaminophen and gentamicin by fluorescence polarization immunoassay (Abbott Laboratories, 1984), \(^{99}\text{Tc}\) activity by \( \gamma \) counting (MR 1032 Automatic Gamma Counting System model 2B W + W Electronics) and correction for radioactive decay, and indocyanine green concentrations.

**Plasma samples**

The assays for acetaminophen were performed the day immediately after the study, whereas the gentamicin samples were stored at 4 °C and assayed in lots of five patients. For both the acetaminophen and gentamicin assays, the plasma was separated immediately before analysis.

Whole blood was assayed for \(^{99}\text{Tc}\) activity. Immediately after the administration of the \(^{99}\text{Tc}\)DTPA, the syringe used for administration was measured for residual activity.

The blood for indocyanine green samples was stored at room temperature until the end of the sampling period and then centrifuged at 8000 rpm for 5 min and the plasma stored in a −80 °C freezer. Samples were assayed in one batch using a UV spectrophotometry (Shimadzu recording spectrophotometer UV/240, Shimadzu Corporation, Kyoto, Japan). Whilst indocyanine green is unstable in water, it is stable in plasma (Becton–Dickinson, Manufacturer’s Information Sheet, 1990) and therefore no correction factor was used when calculating the plasma concentrations.

![Graphs showing acetaminophen plasma concentrations over time](image-url)
Gastrointestinal transit times

Transit times of the acetaminophen/99mTcDTPA mixture along the gastrointestinal tract were calculated using the method of Read, which analyses each frame and determines when the head of the mixture reaches a particular point.\textsuperscript{32}

Data analysis

Model-dependent pharmacokinetic parameters were estimated using the pharmacokinetic program Minim\textsuperscript{8} which was developed in the late 1980s by Dr Robert Purves of the Department of Pharmacology, University of Otago. The Minim\textsuperscript{8} program was used to calculate area under the plasma concentration–time curve (AUC), time to peak concentration (t\textsubscript{max}) and peak concentration (C\textsubscript{max}). A Bioequivalence\textsuperscript{8} program was used in analysis of the data. Student’s paired t-tests were used to compare pre- and postoperative observations. P-values of <0.05 were considered statistically significant.

Results

Acetaminophen plasma concentrations

The mean plasma concentrations in all three studies are shown in Figure 1. Model-independent pharmacokinetic parameters were determined appropriate.

Study I, the i.v. study; establishment of acetaminophen pharmacokinetic parameters after i.v. administration (n=6)

All patients underwent operations for tumour resection of large bowel. There was no significant difference in the pre- and postoperative values for peak concentration (C\textsubscript{max}), time to peak concentration (t\textsubscript{max}), mean residence time (MRT), area under the plasma concentration–time curve (AUC), volume of distribution (V\textsubscript{d}) and clearance (C\textsubscript{L}) (Table 2).

Data were fitted to both one and two compartment bolus infusion models. Except for subject 4 (R\textsuperscript{2}=0.85), a two compartment bolus infusion model was judged a better fit, this judgement being based on the difference between the two models in the residual sum of squares, the Akaike information criterion, and the distribution of the residual errors tests for randomness using the runs test. There were no significant differences in the pre- and postoperative values in α, β and the elimination rate constant, k\textsubscript{21} (Student’s paired t-test; P>0.05).

Study II, the oral study; investigation of oral acetaminophen absorption (n=12)

Two patients underwent operations for abdominal aortic aneurysm repair, 10 for tumour resection of large bowel.

After surgery, the C\textsubscript{max} was approximately half that measured in the preoperative phase [30.2 (2.9) \textmu g ml\textsuperscript{-1} vs 16.3 (2.6) \textmu g ml\textsuperscript{-1}, mean (SEM); Table 3]. In some instances after operation the absorption phase outlasted the blood-sampling phase.

| Study | Age (yr) | M:F | Weight (kg) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubscript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubcript{max} (mg ml\textsuperscript{-1}) | C\textsubipte
Study III, the intraduodenal study; investigation of oral acetaminophen absorption when administered directly into the duodenum (n=12)

Six patients underwent operations for abdominal aortic aneurysm repair, six patients for tumour resection of large bowel.

The $C_{\text{max}}$ was reduced ($P<0.05$) and the $\text{MRT}$ was greater after operation ($P<0.01$). There were no significant differences in the pre- and postoperative values of $t_{\text{max}}, \text{AUC}$ and area under the moment curve (AUMC) before and after operation ($P>0.05$) (Table 3).

The relative bioavailability of acetaminophen was calculated. Although there were some quite wide intra-individual differences in the absorption of acetaminophen in the two phases of the study, overall, there was less than a 20% difference in drug bioavailability ($F_{\text{rel}}=1.09 (0.11)$).

Comparison of oral preoperative and intraduodenal postoperative plasma concentrations

The postoperative absorption of acetaminophen administered intraduodenally was similar to that after oral administration before operation except the $t_{\text{max}}$ value was shorter in the intraduodenal study (Fig. 2).

Gentamicin concentrations

The model-independent pharmacokinetic parameter estimates for gentamicin before and after operation for all studies are shown in Table 4. There were no statistically significant differences in $C_{\text{max}}$ and $V_d$ (litre kg$^{-1}$) ($P>0.05$).

Comparison of gentamicin and acetaminophen data

Following surgery the volumes of distribution of acetaminophen given i.v. and of gentamicin increased modestly but the differences were not statistically significant. There was, however, a significant correlation ($R^2=0.418$, $F=13.9$, $P<0.05$) in these changes between acetaminophen and gentamicin volumes of distribution ($V_d$).

Indocyanine green

Mean pre- and postoperative serum concentrations for indocyanine green ($n=9$) are shown in Figure 3. There was no significant difference between mean indocyanine green concentrations or between the AUCs in the pre- and postoperative phases of the study ($P>0.05$).

Discussion

In a previous study, we demonstrated that the longer surgical patients are without their regular medicines, the

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yr)</th>
<th>M:F</th>
<th>Weight (kg)</th>
<th>$C_{\text{max}}$ (mg ml$^{-1}$)</th>
<th>$t_{\text{max}}$ (min)</th>
<th>MRT (min)</th>
<th>AUC (10$^3$ mg min$^{-1}$ ml$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study II</td>
<td>Mean (range or SEM)</td>
<td>57.6 (41–71)</td>
<td>9:3</td>
<td>70.7 (3.2)</td>
<td>30.2 (2.9)</td>
<td>16.3 (2.6)</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Study III</td>
<td>Mean (range or SEM)</td>
<td>67.8 (52–77)</td>
<td>10:2</td>
<td>71.2 (3.4)</td>
<td>30.7 (2.7)</td>
<td>24.2 (1.4)</td>
<td>21 (5)</td>
</tr>
</tbody>
</table>

Fig 2 Comparison of preoperative oral (open diamonds) acetaminophen and postoperative duodenal (closed diamonds) acetaminophen (1.5 g) in two different patient groups, both undergoing major abdominal surgery (bars=SEM; $n=12$).

$^{99m}$TcDTPA

The mean concentration of the $^{99m}$TcDTPA absorbed before and after surgery is shown in Figure 4. There were substantial but not statistically significant increases in the blood concentrations of $^{99m}$TcDTPA after operation (Student’s paired $t$-test, $P>0.05$). There were no significant differences in the pre- and postoperative values for $C_{\text{max}}$, $t_{\text{max}}$ and AUC$_{0-300}$ for $^{99m}$TcDTPA ($P>0.05$), although there were wide intra-individual differences between the two phases of the study. There was no significant difference in the pre- and postoperative amounts of $^{99m}$TcDTPA excreted over the 5 h period ($P>0.05$).

The transit time of $^{99m}$TcDTPA marker to the ileocaecal valve was increased only a modest amount after surgery. However, in contrast to the preoperative studies, no filling of the ascending colon could be detected after operation for the duration of the scanning period of 1 h. Pooling of acetaminophen/$^{99m}$TcDTPA mixture was noted in the stomach in many of the patients after surgery. Pre- and postoperative scintoscans for a typical patient are shown in Figure 5A and B.

<table>
<thead>
<tr>
<th>Study characteristic and pharmacokinetic parameters, ($C_{\text{max}}, t_{\text{max}}, \text{MRT}, \text{AUC}$) of acetaminophen given in Study II (acetaminophen 1.5 g orally) and Study III (acetaminophen 1.5 g intraduodenally)</th>
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<tbody>
<tr>
<td>Study</td>
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<tr>
<td>Study II</td>
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<tr>
<td>Study III</td>
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more non-surgical complications these patients suffer in the postoperative period. Hence it is reasonable to suggest that these regular medicines should be re-instated as quickly as possible in the postoperative period. Problems with delayed gastric emptying, as a result of surgery and narcotic administration, often preclude this. However, if this impediment to drug delivery is bypassed and drugs are delivered directly into the small intestine, then it is important to know the pattern of absorption and whether the surgical event modifies this.

Three experiments were carried out to answer this question. Study I, the i.v. study, established that there was only a modest change in the volume of distribution of gentamicin and that this was relatively insignificant. What change that there was, correlated with changes in the volume of distribution of gentamicin. Acetaminophen has a much larger volume of distribution (0.94 litre kg⁻¹) and distributes into more than one body compartment when compared with gentamicin (0.25 litre kg⁻¹), the latter paralleling body water distribution. This suggests that the small changes seen in the volume of distribution of acetaminophen were attributable to changes in the extra cellular fluid (ECF) compartment. In addition, there was no change in the other pharmacokinetic parameters (Cmax, MRT, AUC, AUMC, and C1; P>0.05) of i.v. acetaminophen before and after surgery, thus confirming that surgery had little or no effect on the pharmacokinetics of acetaminophen when it was administered i.v.

Study II, the oral study, confirmed the deleterious effect of surgery on the oral absorption of drugs. The majority of drugs are absorbed from the small intestine, thus delays in gastric emptying will have effects on both the maximum concentration (Cmax) and the time taken to reach this (tmax).

Study III, with the administration of the acetaminophen directly into the small bowel, showed not only that the delays resulting from gastric function were avoided but that the absorption from the small bowel was as good as that achieved by the oral route before surgery. Having established in Study I that the Vd and C1 of acetaminophen did not change significantly, we were able to use the formula 

$C_{max}=\frac{F \times \text{dose}}{V_d}$

(where F is bioavailability or fraction absorbed), to assess small bowel absorption after surgery. We found that of acetaminophen, Cmax was significantly reduced after surgery (P<0.05) and the MRT (P<0.01) was increased markedly, indicating that although peak plasma concentration from the small bowel was decreased, the overall amount of acetaminophen absorbed over time was unaffected.

There are several explanations for this lowered postoperative Cmax after duodenal administration of acetaminophen: alterations in Vd, C1, MRT or a change in absorptive ability of the duodenum. It is unlikely to be due to changes in Vd because of the very small changes in volume of distribution observed in Study I. Clearance of acetaminophen in Study I was unaffected and makes this explanation unlikely. Other possibilities include a change in MRT or a slower or decreased absorption from the

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**Table 4** Pharmacokinetic parameters, Cmax, and MRT of gentamicin 80 mg given i.v. in all studies. *Sampling interval different from all others. †Unable to be calculated.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cmax (µg ml⁻¹)</th>
<th>MRT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>Postop</td>
</tr>
<tr>
<td>IV01</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>IV02</td>
<td>5.9</td>
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**Fig 3** Mean plasma pre- and postoperative concentrations of indocyanine green before (open diamonds) and after operation (closed diamonds) after i.v. indocyanine green (0.5 mg kg⁻¹ over 5 min) t=0 min and t=30 min (bars=SEM; n=9).
gastrointestinal tract. The latter two explanations were most probable through either:

(i) a decrease in the permeability of the gastrointestinal tract,
(ii) a modification in portal blood flow thus decreasing the concentration gradient across the gut wall, or
(iii) an alteration in the spread of the acetaminophen mixture throughout the gastrointestinal tract or a reflux back into the stomach.

A decrease in permeability was discounted because the opposite was demonstrated by absorption of 99mTcDTPA that was, if anything, increased after operation although this did not reach statistical significance. This may have been because of insufficient sample size. Increased 99mTcDTPA is consistent with a number of reports of an increase in gut permeability in critically ill and postoperative patients.13 34 35 In addition, aldosterone, which is increased as part of the stress response to surgery, has also been shown to increase paracellular absorption in the rabbit colon.36 These factors would more probably increase Cmax rather than decrease it. Thus a decrease in Cmax of acetaminophen could probably not be attributed to decreased gut permeability.

A reduction in portal blood flow resulting in a decreased concentration gradient across the gut wall is also an unlikely cause. This was shown by indocyanine green dosing. There was no significant difference in the hepatic clearance of this compound from the plasma before and after surgery. This suggests that as hepatic clearance of indocyanine green reflects intestinal blood flow, acetaminophen absorption is unlikely to have been influenced by this after surgery.

Another explanation for a decrease in Cmax, could be a change in gut motility. The spread of the acetaminophen mixture throughout the gastrointestinal tract, was assessed using the spread of the acetaminophen/99mTcDTPA mixture. Clements and colleagues37 used a similar mix of acetaminophen/113mInDTPA to follow the emptying of acetaminophen from the stomach and determine the absorption pharmacokinetics from the small intestine in normal healthy volunteers. By using 60 min of scanning, and taking frames at 5 min intervals, it was possible to compare the difference in spread throughout the gut in each patient before and after surgery. There was no significant difference in pre- and postoperative values in the transit time for 99mTcDTPA to reach the ileocecal valve (P>0.05 Student’s paired t-test). This is in agreement with much of the literature, which supports the fact the small intestine starts functioning again shortly (6 h) after surgery.1–3 11 The presence of small bowel motility after operation, is reassuring with respect to drug absorption, as gut motility provides close contact of the drugs with the brush border membrane.38 Thus a lowered Cmax probably did not result from a difference in spread of the acetaminophen mixture through the small bowel and this is supported by work from Ueno and colleagues39 who concluded that most of an oral dose of acetaminophen is absorbed in the jejunum, distal to the duodenojejunal flexure, when patients have a normal intact gastrointestinal tract.

The remaining possible explanation for a decreased Cmax is the possible loss of acetaminophen from the absorptive surface of the duodenum as a result of reflux back into the stomach. Acetaminophen is not absorbed in the stomach, the reason for its use as a marker of gastric emptying. This
reflux was indeed the case as shown by the postoperative scintiscans (Fig. 5) with duodenal reflux and pooling in the stomach of some of the acetaminophen/99mTc solution in the postoperative phase of the study observed. No duodenal reflux was seen in any patient in the preoperative phase of the study. As all studies (before and after operation) were undertaken in the same position, the effect of posture at the time of scanning, can be discounted as a reason for
reflux into the stomach. Reflux may have occurred through the way the patients were lying in bed after surgery or through a disordinated migrating motor complex in the duodenum and a consequent retropulsive action, sending the liquid back into the stomach. The pylorus seemed to allow fluid back into the stomach but once it was in the stomach, it remained there. This is further substantiated by the increase in MRT. MRT, another measure of drug elimination, is the average time a drug molecule remains in the body after rapid i.v. injection. Its value is independent of dose. In Study I, the i.v. study, MRT was unchanged, but markedly increased (P<0.01) in the intra-duodenal study, thus indicating acetaminophen remained in the body for a longer period of time because the acetaminophen became ‘trapped’ in the stomach and was unable to be absorbed into the systemic circulation, from where it was subsequently eliminated.

Despite this, the direct duodenal route proved the most effective route for administering a drug, such as acetaminophen to patients early in the postoperative period. The Cₘₙₓ attained is comparable with that normally seen in the non-surgical situation when the drug is taken by mouth. Acetaminophen is a useful model drug because it is absorbed only from the small intestine, a situation for the majority of drugs, has a high oral bioavailability (F=0.88) and is an indicator of gastric emptying. Our study suggests that small bowel absorption is normal after surgery for this and similar drugs such as the cardiovascular drugs, used prevalently in a surgical population. More aggressive approaches to delivery of drugs into the small bowel via gastroduodenal tubes, feeding nasojejunal tubes or feeding jejunostomies will not only have advantages for nutritional support but also for adequate drug delivery. Savings by avoiding the i.v. route could be made.

For the majority of lipophilic drugs, no dose alteration from the usual oral route is recommended when using the duodenal route. There is some note of caution, however, regarding drugs that have a narrow therapeutic window and because of the significantly shortened tₘₙₓ, where too rapid an increase in the plasma concentration may have deleterious effects. Calcium antagonists are such a case in point.

The use of nasogastric tubes in intensive care and surgical patients is not unusual. A common practice is to use these as a route for drug administration, but this is not without hazards, nor does it guarantee comparative plasma concentrations obtained from oral administration when patients are well. Delays in gastric emptying in such patients decrease transfer of drug to the small intestine, resulting in diminished peak plasma concentrations. This has been clearly demonstrated in this study and others. In contrast, drug absorption from the small bowel after surgery is largely unaffected for drugs such as acetaminophen. While there is some reduction in Cₘₙₓ this peak plasma concentration was reduced as a result of solution reflux back into the stomach. The intraduodenal route could or should more often be used to effect early reintroduction of regular medicines to patients in the early postoperative period, thus reducing the increased risk of morbidity caused through lack of withdrawal of essential medication.

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