THE ABSORPTION, PHARMACODYNAMICS, METABOLISM AND EXCRETION OF $^{14}$C-SUMATRIPTAN FOLLOWING INTRANASAL ADMINISTRATION TO THE BEAGLE DOG

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ABSTRACT

The pharmacodynamics, pharmacokinetics, metabolism, and excretion of $^{14}$C-sumatriptan have been studied in the beagle dog following administration by the intranasal and other routes. The pharmacological response which was monitored, an increase in carotid arterial vascular resistance, correlated with the plasma levels of unchanged sumatriptan following intranasal, intravenous, or intraduodenal administration to the anaesthetised dog. The pharmacokinetics and metabolism of sumatriptan were then confirmed in conscious male and female dogs. Intranasal administration of $^{14}$C-sumatriptan resulted in rapid absorption of part of the dose. The overall bioavailability of sumatriptan was 40–50%. Sumatriptan was eliminated from plasma with a half-life of 1.5 or 1.9 h after intravenous or intranasal dosage respectively. Radioactivity was largely excreted in urine (up to 75% of the dose) with small amounts in the bile and faeces after intravenous and intranasal dosing, as sumatriptan and a major metabolite. The results from these studies suggest that intranasal administration provides a viable method for delivering sumatriptan to the systemic circulation.

KEY WORDS: sumatriptan; beagle dog; intranasal; pharmacokinetics; pharmacodynamics.

INTRODUCTION

Sumatriptan (GR43175; 3-[2-diethylaminoethyl-N-methyl-1H-indole-5-methane-sulphonamide; Figure 1) is a novel 5-HT$_{1D}$-receptor agonist used in the treatment of migraine and cluster headache.$^{1,2}$ Sumatriptan is an effective and

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well tolerated acute treatment for migraine when given by oral or parenteral routes. However, a substantial proportion of patients suffer severe nausea or vomiting during their migraine attack which may make oral treatment unsatisfactory. Subcutaneous administration is an alternative, but dislike of injections or inability to self-administer by this route makes subcutaneous treatment unacceptable to some individuals. The intranasal route may be a viable alternative route of self administration whereby these limitations could be overcome.

Sumatriptan has previously been shown to have a low to moderate oral bioavailability in laboratory animals (rabbits, 23%; rats, 37%; dogs, 58%) and in human volunteers (14%). It is metabolized by human monoamine oxidase-A to an indole acetic acid metabolite (GR49336; Figure 1). Although the nasal mucosa of animals and man contain drug metabolizing enzymes capable of oxidative function any presystemic metabolism of sumatriptan may be less extensive after intranasal dosing than that observed after oral dosing.

The present studies were carried out to investigate the feasibility of utilizing the intranasal route of administration using the beagle dog as a model for man. Although there are species differences between animals and man in regard to the nasal cavity the metabolic disposition of sumatriptan after parenteral dosage to dogs was comparable to that in man. An anaesthetized dog model has previously been used to monitor the changes in a pharmacological response, carotid arterial vascular resistance, following administration of sumatriptan. In an initial study the effects of 14C-sumatriptan on carotid arterial vascular
resistance were determined following intranasal administration of two experimental formulations and compared to the effects observed after intravenous or oral administration. Preliminary data on the metabolic disposition of the compound were also obtained. As the data from this initial study was obtained from single animals only, thus giving no indication of variability, and as the viability of this model does not extend beyond about 6 h, definitive pharmacokinetic and metabolism information were then obtained from a further study using conscious dogs. For this second study an intranasal formulation of 14C-sumatriptan comparable to the proposed clinical formulation for use in man was administered to male and female dogs.

MATERIALS AND METHODS

Pharmacodynamic/disposition studies in anaesthetized dogs

Beagle dogs (7–11 kg, GW R&D) of either sex were fasted overnight and anaesthetized with barbitone following induction with thiopentone (25 mg kg\(^{-1}\) i.v.) and pentobarbitone (60 mg i.v.). Animals were artificially respired with room air at a rate of 20 strokes min\(^{-1}\) and a stroke volume of 13–16 mL kg\(^{-1}\) adjusted to maintain arterial blood gases within normal physiological limits. Body temperature was maintained at 39–40 °C. Arterial blood pressure was recorded from a cannulated femoral artery and heart rate derived from the blood pressure signal; right common carotid artery blood flow was recorded using an electromagnetic flow probe (2.5 mm, Statham). Carotid arterial vascular resistance (CAVR) was calculated by dividing the mean arterial blood pressure by the mean carotid artery blood flow. The left femoral vein was cannulated for the intravenous administration of sumatriptan (or of 14C-sumatriptan to one dog) or supplementary anaesthetic as required. The right femoral vein was cannulated for the withdrawal of venous blood samples. The dog which received 14C-sumatriptan by the intraduodenal route of administration was implanted with a fine cannula (o.d. 0.5 mm, Portex) inserted approximately 2 cm into the proximal duodenum via a small incision in the upper abdominal wall.

After a stabilization period the basal pharmacological parameters were recorded and a control sample of venous blood was removed. The volume of each blood sample withdrawn was immediately replaced with dextran 110 (6% w/v in sodium chloride). Blood samples were collected into heparinized vials and the plasma separated by centrifugation (MSE 6L Coolspin, 1720 g, 15 min, 4 °C).

Each dog then received a single dose of 14C-sumatriptan at a dose equivalent to approximately 1 mg base kg\(^{-1}\) by either the intravenous (14C-sumatriptan as the succinate salt in saline solution; dose volume approximately 1 mL), intraduodenal (14C-sumatriptan as the succinate salt in distilled water, dose volume 0.5 mL washed into the duodenum with 0.5 mL saline solution), or intranasal (14C-
sumatriptan as the succinate salt in saline solution pH 4.7 or as the base suspended in sodium bicarbonate solution pH 10.5) route of administration. The intranasal doses were applied using a syringe and needle with Portex PP30 tubing attached. Approximately 0.1 mL was instilled 1.5 cm into each nostril.

Blood samples were removed at 5, 15, 30, 45, 60, 75, 90, 120, 150, 180, and 240 min after dosing for the determination of unchanged sumatriptan and radioactivity in plasma, and pharmacological measurements were recorded at these time points. Four hours after administration of each dose of $^{14}$C-sumatriptan, a cumulative intravenous dose–response curve (0.03–1 mg kg$^{-1}$) for sumatriptan was established to determine the maximum increase in CAVR for each individual dog. Thus in each dog the increase in CAVR produced by $^{14}$C-sumatriptan was expressed as a percentage of the maximum increase in CAVR produced by sumatriptan following intravenous dosing.

At the end of each experiment, urine and bile samples were collected for analysis of excreted radioactivity to determine the metabolite profile by radiochromatography.

**Disposition studies in conscious dogs**

Beagle dogs, (three male, three female) were housed in standard metabolism cages which permitted the separate collection of urine and faeces, and allowed access to water and to commercial pellet diet *ad libitum*. Dogs were dosed intranasally or intravenously with an aqueous solution of $^{14}$C-sumatriptan in a buffered media, pH 5.4–5.6. Blood, urine, and faeces were collected for selected times up to 168 h post-dose.

**Analytical methods**

The radioactivity content of the biological samples was determined either by direct liquid scintillation counting or after combustion procedures, with appropriate quench correction. Plasma samples were precipitated with acetone and centrifuged and the supernatants concentrated under nitrogen at room temperature.

Aliquots of diluted dosing solution, urine, bile, and extracts of plasma were investigated by thin-layer radiochromatography (TLRC) and/or high-performance liquid radiochromatography (HPLRC). The TLRC analyses were carried out using silica gel 60F254 plates (Merck) which were developed in the following solvent mixtures:

(A) ethylacetate–isopropanol–water–0.88 w/w ammonia solution (50:30:16:4);
(B) dichloromethane–ethanol–0.88 w/w ammonia solution (80:16:2); and
(C) ethylacetate–methanol–0.88 w/w ammonia solution (56:36:8).

The HPLRC analyses were carried out using Radial-Pak CN-10 columns (10 cm $\times$ 0.8 cm fitted with CN Guard-Pak precolumns (Resolve TM, Waters
Chromatography) by gradient elution using 0.025 M ammonium acetate pH 4.3 (solvent A) and acetonitrile (solvent B) at a flow rate of 2 mL min⁻¹. Radioactivity was detected and quantified using an Isomess 3000 detector or a Ramona LS4 radiodetector with a 6800 data system (Raytest Ltd). Samples of control biological matrix-extract or matrix-extract fortified with ¹⁴C-sumatriptan or solutions of sumatriptan or of ¹⁴C-sumatriptan or of GR49336 were analysed with the the experimental samples.

The plasma concentrations of unchanged sumatriptan were quantified using either a cation-exchange method¹⁰ or an HPLC method.¹¹

**Analysis of data**

The plasma concentration data for the individual male and female dogs were calculated and the \( C_{\text{max}} \) and \( t_{\text{max}} \) values obtained by inspection. The data were analysed for pharmacokinetic parameters using the SIPHAR interactive pharmacokinetics program (SIMED) which derives clearance from dose/area under curve (AUC) values. The AUC values were also derived for the equivalent concentrations of total drug-related material (radioactivity) in plasma. Mean parameters were calculated for the three male and for the three female dogs in the pharmacokinetic and metabolism study.

The percentage of total dose (radioactivity) excreted in the urine, bile, or faeces was calculated for the periods 0–5 h (anaesthetized dogs) and 0–168 h (conscious dogs).

**Chemicals**

Sumatriptan base (GR43175X; Figure 1) and sumatriptan succinate (GR43175C) were obtained from the Pharmacy Division of GlaxoWellcome R & D (GW R&D). Sumatriptan radiolabelled with ¹⁴C in alternative positions (see versions A and B, Figure 1) was obtained from the Radioisotope Laboratory, GW R&D, as either the free base or succinate salt forms. The metabolite, GR49336X (Figure 1), was supplied by the Process Research Dept, GW R&D. Chemicals used in the preparation of reagents and buffers, and solvents used in TLC or HPLC analyses, were of Analar grade and obtained from recognised suppliers. All drug dilutions were made in 0.9% saline solution unless otherwise stated and all doses of drug refer to the free base.

**RESULTS**

**Pharmacological response and plasma sumatriptan**

The intravenous administration of ¹⁴C-sumatriptan (1 mg kg⁻¹) to the anaesthetized dog caused an immediate increase in CAVR (100% intravenous maximum response at 1 min post-dose) which declined rapidly to 24%
intravenous maximum response after 1 h. Over the next 3 h the level of vasoconstriction remained fairly constant (15–25% intravenous maximum response). The plasma concentration of sumatriptan also decreased rapidly, from 2860 ng mL$^{-1}$ at 2 min to 210 ng mL$^{-1}$ at 1 h and then to 74 ng mL$^{-1}$ at 4 h post dosing. (See Figure 2.)
Following intraduodenal administration of $^{14}$C-sumatriptan (1 mg kg$^{-1}$) to the anaesthetized dog, CAVR increased rapidly during the first hour, from a 7% increase at 5 min to a 101% increase at 1 h then slowly declined to 59% at 4 h after dosing. The plasma concentration of sumatriptan increased rapidly over the first hour after dosing, from 6 ng mL$^{-1}$ at 5 min to 96 ng mL$^{-1}$ at 1 h, then declined over the next 3 h to 46 ng mL$^{-1}$. (See Figure 3.)

Following intranasal administration of $^{14}$C-sumatriptan (1 mg kg$^{-1}$) in solution at pH 4.7, CAVR increased rapidly over the first 45 min, from a 12% increase at 5 min to a 63% increase at 45 min after dosing, and then remained fairly constant over the next 3 h (61–75% increase). The plasma concentration of sumatriptan increased rapidly over the first 45 min, from 6 ng mL$^{-1}$ at 5 min to 96 ng mL$^{-1}$ at 1 h, then declined over the next 3 h to 46 ng mL$^{-1}$.
concentration of sumatriptan increased from 27 ng mL$^{-1}$ at 5 min to 96 ng mL$^{-1}$ at 45 min after dosing and then remained reasonably constant over the next 3 h (between 92 and 107 ng mL$^{-1}$). (See Figure 4.) Following intranasal administration of $^{14}$C-sumatriptan (1 mg kg$^{-1}$) in suspension at pH 10·5, CAVR increased rapidly from a 12% increase at 5 min to a 99% increase at 30 min after dosing and then declined slowly to 56% 4 h after dosing. The plasma concentration of sumatriptan increased rapidly during the first 45 min after dosing from 8 ng mL$^{-1}$ at 5 min to 187 ng mL$^{-1}$ at 30 min and then declined to 51 ng mL$^{-1}$ at 4 h. (See Figure 5.)
Pharmacokinetics (anaesthetized and conscious dogs)

The pharmacokinetic parameters derived from the plasma concentration data for unchanged sumatriptan and radioactivity from single anaesthetized dogs (see Table 1) indicate that less than 50% of the intraduodenal dose and less than 50% of either of the intranasal formulations was absorbed within 4 h after dosing. The bioavailability of sumatriptan was estimated as 29% (intraduodenal), 38% (intranasal solution, pH 4.7), and 41% (intranasal suspension, pH 10.5). The calculated elimination half-life for sumatriptan was comparable (1.5, 1.8 h) after intravenous and intranasal suspension dosage.
but increased (2.9 h) after intraduodenal administration. It was not possible to calculate an elimination half-life for the intranasal solution at pH 4.7.

Following intravenous administration of $^{14}$C-sumatriptan (1 mg base kg$^{-1}$) to conscious dogs, unchanged sumatriptan was shown to be rapidly eliminated from plasma with a half-life of approximately 1.4 h (see Table 2). After intranasal instillation of an aqueous solution of $^{14}$C-sumatriptan at pH 5.5, the plasma levels increased from below 20 ng mL$^{-1}$ at 5 min to approximately 150 ng mL$^{-1}$ (male dogs) or 120 ng mL$^{-1}$ (female dogs) at 30 min after dosing. The plasma concentration of unchanged sumatriptan then declined to approximately 20 ng mL$^{-1}$ at 6 h post-dose with a calculated half-life of approximately 1.9 h (see Table 2). In one female dog, a second peak of sumatriptan in plasma was observed, representing 101 ng mL$^{-1}$ at 2 h after dosing. The apparent bioavailability of sumatriptan was calculated as approximately about 44% for both male and female dogs.

Levels of radioactivity (representing drug and metabolites in plasma) were detected up to 24 h after intranasal administration. From a comparison of the AUC data (i.n./i.v.) it appears that the absorption of the intranasal dose was complete over this period.

### Table 1. Derived pharmacokinetic parameters for sumatriptan and radioactivity in the anaesthetized dog following administration of $^{14}$C-sumatriptan (form A (Figure 1) was used; 1 mg base kg$^{-1}$) by the intravenous, intraduodenal, and intranasal routes

<table>
<thead>
<tr>
<th></th>
<th>Intravenous</th>
<th>Intraduodenal (pH 4.7)</th>
<th>Intranasal (pH 4.7)</th>
<th>Intranasal (pH 10.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta$</td>
<td>$\delta$</td>
<td>$\varphi$</td>
<td>$\delta$</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng mL$^{-1}$)</td>
<td>2859</td>
<td>96</td>
<td>96</td>
<td>187</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.03</td>
<td>1.00</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>AUC$^a$ (ng h$^{-1}$mL$^{-1}$)</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>$V_d$ (mL kg$^{-1}$)</td>
<td>15</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.5</td>
<td>2.9</td>
<td>NC$^b$</td>
<td>1.8</td>
</tr>
<tr>
<td>$F$ (%)</td>
<td>—</td>
<td>29</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>$C_{\text{max}}$/AUC (h$^{-1}$)</td>
<td>—</td>
<td>0.35</td>
<td>0.27</td>
<td>0.48</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.8</td>
<td>4.5</td>
<td>NC</td>
<td>2.9</td>
</tr>
<tr>
<td>Radioactivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng Eq. mL$^{-1}$)</td>
<td>—</td>
<td>235</td>
<td>206</td>
<td>246</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.03</td>
<td>1.75</td>
<td>3.00</td>
<td>1.00</td>
</tr>
<tr>
<td>AUC$^a$ (ng Eq. h mL$^{-1}$)</td>
<td>1789</td>
<td>718</td>
<td>544</td>
<td>840</td>
</tr>
<tr>
<td>Absorption (%)</td>
<td>—</td>
<td>40</td>
<td>30</td>
<td>47</td>
</tr>
</tbody>
</table>

$^a$AUC values for 0–4 h only.

$^b$Values could not be calculated.
Excretion balance studies (anaesthetized and conscious dogs)

The amounts of radioactivity excreted in the urine and bile (anaesthetized dogs) and in urine and faeces (conscious dogs) are shown in Tables 3 and 4 respectively. The urine collected for times up to 5 h from the individual anaesthetized dogs contained variable amounts of radioactivity (18–62% total dose) and bile contained only small amounts (2–4% total dose) at the termination of the experiment. The total amount of radioactivity excreted was greater after intravenous dosing (66%) than after intraduodenal or intranasal dosing.

Following both intravenous and intranasal administration of ¹⁴C-sumatriptan in aqueous solution at pH 5.5 to conscious dogs radioactivity was primarily excreted in urine within 24 h (Table 4). After intravenous dosing an average of 62 or 60% for the male or female dogs respectively was excreted in urine with 8.5 or 5.2% respectively excreted in faeces. After intranasal dosing, the amount of sumatriptan excreted in urine and faeces was 65 and 16% respectively in males and 66 and 13% respectively in females. A comparison of the urinary excretion data (i.n./i.v.) suggests that the intranasal dose was almost completely absorbed.
Metabolic profiles (anaesthetized and conscious dogs)

In the study with anaesthetized dogs, the metabolite profiles for urine, bile, and extracts of plasma were qualitatively similar following each route of administration (data not shown). Unchanged sumatriptan and a major metabolite which co-chromatographed with GR49336 were observed in all fluids with minor amounts of three or four other radiolabelled components. In urine, 47–64% of the radioactivity (8–32% dose) co-chromatographed with GR49336 and 31–49% of the radioactivity (9–27% dose) with unchanged sumatriptan. The proportion of the radioactivity in urine present as unchanged sumatriptan was lower after intraduodenal dosing (31%) compared to intravenous or intranasal dosing (41–49%). In bile between 76 and 81% of the radioactivity (or 2–3% dose)

Table 3. Excretion of radioactivity in the urine and bile of single anaesthetised dogs following administration of [14C]-sumatriptan (form A (Figure 1) was used; 1 mg base kg⁻¹) by the intravenous, intraduodenal, or intranasal routes, expressed as percentage of total dose excreted

<table>
<thead>
<tr>
<th></th>
<th>Intravenous</th>
<th>Intraduodenal</th>
<th>Intranasal pH 4·7</th>
<th>Intranasal pH 10·5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>♂</td>
<td>62</td>
<td>32</td>
<td>18</td>
<td>39</td>
</tr>
<tr>
<td>♀</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>35</td>
<td>20</td>
<td>42</td>
</tr>
</tbody>
</table>

Table 4. Excretion of radioactivity in the urine and faeces of conscious male and female dogs following administration of [14C]-sumatriptan (form B (Figure 1) was used; 1 mg base kg⁻¹) by the intravenous or intranasal routes expressed as mean percentage dose

<table>
<thead>
<tr>
<th></th>
<th>Intravenous</th>
<th>Intranasal pH 5·5</th>
</tr>
</thead>
<tbody>
<tr>
<td>♂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine 0–6 h</td>
<td>41·2 (22·4)</td>
<td>10·8 (18·6)</td>
</tr>
<tr>
<td>6–24 h</td>
<td>18·9 (10·4)</td>
<td>46·8 (25·6)</td>
</tr>
<tr>
<td>0–168 h</td>
<td>61·6 (21·5)</td>
<td>59·8 (26·7)</td>
</tr>
<tr>
<td>Faeces 0–168 h</td>
<td>8·5 (0·6)</td>
<td>5·1 (1·3)</td>
</tr>
<tr>
<td>Cage wash</td>
<td>18·2 (19·3)</td>
<td>21·2 (27·3)</td>
</tr>
<tr>
<td>Total</td>
<td>88·3 (1·9)</td>
<td>86·1 (0·5)</td>
</tr>
</tbody>
</table>

*Includes a value of 1·1% total dose recovered in nasal swabs.

Metabolic profiles (anaesthetized and conscious dogs)

In the study with anaesthetized dogs, the metabolite profiles for urine, bile, and extracts of plasma were qualitatively similar following each route of administration (data not shown). Unchanged sumatriptan and a major metabolite which co-chromatographed with GR49336 were observed in all fluids with minor amounts of three or four other radiolabelled components. In urine, 47–64% of the radioactivity (8–32% dose) co-chromatographed with GR49336 and 31–49% of the radioactivity (9–27% dose) with unchanged sumatriptan. The proportion of the radioactivity in urine present as unchanged sumatriptan was lower after intraduodenal dosing (31%) compared to intravenous or intranasal dosing (41–49%). In bile between 76 and 81% of the radioactivity (or 2–3% dose)
co-chromatographed with GR49336 but only 6–13% of the radioactivity (1% dose, or less) co-chromatographed with sumatriptan.

Analysis of extracts of plasma confirmed that sumatriptan was the major component in the extracts, with some GR49336 and minor amounts of three or four other metabolites.

Analysis of the urine for 0–24 h after dosing from the three male and three female conscious dogs which received 14C-sumatriptan by the intravenous or intranasal routes showed that GR49336 and unchanged sumatriptan were the major radiolabelled components in the samples, irrespective of the route of administration. Up to seven other minor components were detected in urine. The amounts of the two major and seven minor components varied with each animal and there was no indication of a gender-linked difference.

DISCUSSION

The aim of these studies was to confirm that sumatriptan would be absorbed after intranasal administration. The beagle dog was chosen as the model species as the dog had been previously used to study the pharmacodynamics, toxicology, and the metabolic disposition of sumatriptan by other routes of administration. The dog has been shown to be comparable to man with regard to the metabolism and pharmacokinetics of sumatriptan.3,5 Pharmacodynamic studies were carried out in anaesthetized dogs and pharmacokinetic and metabolic information was obtained from studies in conscious and anaesthetized dogs.

The shape of the pharmacological effect curve (CAVR measurement) and the plasma sumatriptan concentration curve were similar following each route of administration, suggesting that there is some correlation between the pharmacological effect and plasma concentration. However, comparison between each route of administration did not reveal a direct correlation between the actual plasma concentration and the pharmacological effect. For example, when the concentration of sumatriptan was about 100 ng base mL$^{-1}$ there was a 100% increase in CAVR after intraduodenal dosage but only a 20% increase after intravenous dosage.

In this study, it has also been shown that the two experimental intranasal formulations (a solution at pH 4·7 and a suspension at pH 10) delivered lower levels of sumatriptan to the systemic circulation than did the intravenous formulation. There were also differences in the shape of the CAVR and plasma sumatriptan concentration curves between the two intranasal formulations. The formulation at pH 10 delivered higher plasma concentrations initially, which were eliminated with a half-life comparable to that found after intravenous dosage. The intranasal formulation at pH 4·7 gave profiles for plasma sumatriptan concentration and CAVR which remained relatively constant for about 3 h after the maximum concentration had been attained, and were more akin to the intraduodenal profiles than to the intravenous profiles.
The absorption of radioactive dose was greater after the intranasal suspension at pH 10 (47%) than after either intranasal solution at pH 4.7 or the intraduodenal dose. This was confirmed by the relative amounts of radioactivity excreted in urine within 5–6 h. The bioavailability of sumatriptan was also greater with the intranasal suspension formulation at pH 10 (48%) than with either the intranasal formulation at pH 4.7 or after intraduodenal dosage.

As this initial study was carried out in anaesthetized dogs and used only single animals, the data obtained were limited but indicated that intranasal administration would represent a viable route for delivering sumatriptan to the systemic circulation. Although clearance of nasal mucus is not affected by anaesthesia in the dog,12 it was decided to confirm the pharmacokinetic and metabolism data using conscious male and female dogs. The formulation chosen for this second study was comparable to the proposed clinical formulation (an aqueous buffered solution of sumatriptan as the hemisulphate salt). This formulation is at pH 5.4–5.6 which is within the normal range of pH for nasal secretions in adult humans9 and is hypertonic. Sumatriptan is highly soluble in this formulation and so concentrated solutions suitable for the administration of small volumes by the intranasal route are practicable. In addition studies using the rat as the model species have shown that intranasal formulations at alkaline pH cause significant membrane and intracellular enzyme release at pH 10 and above13 and so might cause irritation in the nasal mucosa.

Following the intranasal administration of 14C-sumatriptan to dogs using this acidic formulation, the radioactive dose was shown to be well absorbed, delivering plasma concentration levels of unchanged sumatriptan above 100 ng base mL$^{-1}$ within 30 min of dose instillation. Sumatriptan was cleared from plasma with a mean half-life of about 1.9 h, which was longer than the mean half-life calculated following intravenous dosage. The pharmacokinetic parameters calculated after intravenous dosing were comparable to those previously reported for single-dose parenteral studies in dogs with 14C-sumatriptan as the succinate salt.3

Sumatriptan is a basic compound ($pK_a$ 9.63) which is hydrophilic (log $K_{ow}$ of −2.3 for a solution of $1 \times 10^{-2}$ mol L$^{-1}$ at pH 7.0). In reviewing intranasal absorption mechanisms, McMartin et al.14 and Fisher15 have proposed that low-molecular-weight hydrophilic compounds are primarily absorbed by paracellular absorption involving passive diffusion through aqueous channels or pores. If absorption of sumatriptan were dependent solely on the amounts of unionized compound present in the formulation, as suggested by the pH partition hypothesis, then the suspension formulation at pH 10 should deliver significantly more sumatriptan to the systemic circulation than the formulations at either pH 4.7 or 5.5. In fact the plasma levels are only about twice those found with the acidic formulations.

The extent of intranasal absorption would also depend on the length of time that sumatriptan was retained in contact with the nasal mucosa.14 The dose volumes used in these studies were up to 100 $\mu$L per nostril. A check on the
leakage of radioactivity following intranasal dosage showed that less than 4% leaks back out of the nasal cavity within 2 h (data not shown). Retention within the nasal cavity would be controlled primarily by nasal mucociliary clearance. Some part of the dose would be cleared into the pharynx and swallowed with saliva and become a secondary oral dose.

There is some evidence that this occurred with sumatriptan in the present studies. In one conscious dog which received intranasal sumatriptan, a secondary plasma concentration peak was found at 2 h after dosage. The absorption of a gavage dose of sumatriptan is relatively rapid in conscious dogs with the maximum concentrations being observed at about 90 min. The half-life of sumatriptan following intranasal dosage of the formulation at pH 5·5 was also longer than the intravenous half-life. Furthermore, in the one anaesthetized dog dosed intranasally with sumatriptan at pH 4·7, the plasma concentration did not decline for some 3 h after the initial peak plasma concentration had been reached. These observations suggest that a variable amount of secondary oral absorption occurs, thus adding sumatriptan to the systemic circulation whilst the compound already present in plasma after the initial transnasal absorption is being eliminated from plasma.

The excretion of radioactivity and the metabolic profiles after intranasal or intravenous administration were qualitatively similar. That part of the intranasal dose which is absorbed is metabolized to GR49336 and excreted primarily in urine, and to a minor extent in bile and then faeces. There was no evidence for gender linked differences in metabolism or excretion of sumatriptan in this study. The overall bioavailability of sumatriptan after intranasal dosage was about 44% in the conscious dog which suggests that sumatriptan undergoes some first-pass metabolism.

In conclusion, these studies have shown that in beagle dogs the intranasal administration of sumatriptan delivers concentrations of sumatriptan associated with a significant pharmacological response. Overall the absorption of the dose is largely complete but part of the intranasal dose is swallowed after mucociliary clearance and so will be absorbed orally. Sumatriptan is extensively metabolized and both the unchanged drug and its metabolites are excreted largely in urine. The overall bioavailability is estimated as about 44%. The results from these studies indicate that the intranasal route would be an appropriate route for the delivery of sumatriptan in the treatment of migraine. Initial clinical trials with a formulation at pH 5·5 have shown that sumatriptan nasal spray is well tolerated, and delivers peak serum concentrations within 2 h of administration.

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