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Absorption of ipsapirone along the human gastrointestinal tract

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Isapirone·HCl (5 mg) was administered orally, rectally and locally, by a remote control drug delivery device (HF-capsule) into different segments of the gastrointestinal tract, to four young healthy male adults. The relative systemic bioavailability of the drug from the colon and rectum was 2–3-fold greater than that from the upper gastrointestinal tract. This supports a rationale for a prolonged-release formulation.

Keywords ipsapirone azapirones absorption HF-capsule drug delivery device rectal application human gastrointestinal tract sustained release

Introduction

Ipsapirone, a pyrimidinylpiperazine derivative, has anxiolytic [1] and antidepressant [2] properties presumed to be mediated by high affinity binding to 5-HT_{1A} receptors [3].

In man, ipsapirone has an absorption half-life of less than 0.25 h and an elimination half-life ranging from 1–3 h [4, 5]. The rapid increase of its plasma concentration following oral administration in solution is often accompanied by vertigo, dizziness and dysphoria [5], effects which should be avoided by formulating the drug in a modified release preparation.

Prior to the development of such a formulation, it is necessary to assess the relative systemic bioavailability of the drug from different regions of the gastrointestinal tract. Drugs, such as frusemide and ciprofloxacin [6, 7], which are absorbed almost exclusively in the upper gut, have poor availability from prolonged-release dosage forms. In contrast, drugs undergoing extensive first-pass metabolism may demonstrate an increased bioavailability when released in lower gut segments, as has been described for the dihydropyridine derivative nitrendipine [8]. Local differences in a gut wall metabolism are the most probable reason for such an increase.

Substantial first-pass metabolism is said to account for the 10% oral bioavailability of ipsapirone observed in dogs [5]. Thus, the aim of the present study was to evaluate the absorption of ipsapirone along the human gastrointestinal tract to provide data which might support the development of a prolonged-release formulation.

Methods

Four healthy male non-smokers aged 26 ± 2 s.d. years and weighing 70 ± 12 s.d. kg took part in the study. They did not take any medication within 7 days preceding the study, and gave their written informed consent. The study was approved by the Ethics Committee of the University Hospital Frankfurt am Main, Germany.

The study consisted of two parts. Initially, single ascending doses of 1, 2.5 and 5 mg ipsapirone·HCl in aqueous solution (5 ml) were given rectally on one occasion each to all subjects. This was done to find an appropriate dose which was well tolerated even after administration to lower gut segments, since from there a much higher bioavailability than following oral intake could not be excluded (see above). Rectal doses were administered as an enema using a special 5 ml tube (Pharmacia AS, Hillerød, Denmark).

Single 5 mg doses of ipsapirone·HCl were given as an aqueous solution (200 ml) at the start ('oral1') and end ('oral2') of the second part of the study. In between these two periods, the same doses were administered on different occasions to the stomach, small intestine, colon ascendens, and colon transversum or descendens using an HF-capsule [9]. Individual doses were determined by weighing the drug application systems. The planned wash-out period between each administration was 1 week but, because of capsule failure, this was prolonged to several months.

The HF-capsule used was a remote control device for local drug delivery in the gastrointestinal tract

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[9]. It consisted of a polyurethane hull (length: 2.5 cm, diameter: 0.7 cm) containing a small latex balloon as a drug reservoir and a simple mechanism for destruction of the balloon by an external electromagnetic HF signal. The ipsapirone·HCl solution used (5 mg in 0.7 ml) penetrated the hull through small gaps after triggering the release and the hull itself was excreted in the faeces. Part of the capsule and the release mechanism were radioopaque. This enabled localisation in the gastrointestinal tract and checking of successful release by radioscopy. The device was swallowed with 200 ml water.

The HF-capsule was given between 06.00 h (for planned release into colon descendens) and 15.30 h (for stomach release). The first radioscopy was done at 15.30 h, except when the capsule had just been given. If the HF-capsule had reached a site that had not already been studied, drug release was triggered immediately irrespective of the planned site of release and confirmed by a second radioscopy. Otherwise, movement of the device was monitored by radioscopy every 30–90 min until an appropriate site was reached. We used this procedure to mimimize exposure to X-rays. As a result it was not possible to randomise the release sites.

Standard meals were given at predefined times during each study period in an attempt to decrease variation in gastrointestinal transit time. Plasma and saliva samples for measurement of ipsapirone concentrations were taken after capsule intake but prior to release to check for premature drug release (rupture of the latex balloon). The gastrointestinal transit times of the capsule from intake to the application site and to excretion were noted.

The subjects were observed for drug effects up to 15 h after drug administration. Serial blood samples were taken up to 4 h after rectal drug administration, and up to 15 h after dosage with oral solution and the HF-capsule. Urine was collected up to 15 h after oral and HF-capsule administration.

Separated plasma (1 ml) was extracted at pH 7.0 with diethyl ether (10 ml) after adding buspirone (100 ng) as internal standard. After evaporation of the ether phase and reuptake in mobile phase, the drug was assayed by h.p.l.c. using a reversed phase C18 h.p.l.c. column (Nucleosil RP18 5 μm, 125 × 4.6 mm; Bischoff, Leonberg, Germany) with pH 7 phosphate buffer (10 mM):methanol:acetonitrile (42.5:54.5:3 v/v/v, flow rate 1.5 ml min^{-1}) and quantitated by electrochemical detection (ESA Coulochem, coulometric cell) at 0.75 mV. The limit of quantitation was 2.4 ng ml^{-1}. The inter-assay coefficient of variation was 2.8% at 50 ng ml^{-1}, 6.5% at 10 ng ml^{-1} and 11.2% at the limit of quantitation.

Values of AUC were estimated using the linear trapezoidal rule with extrapolation to infinity from C_{last}/λ_z. The terminal elimination rate constant was estimated by linear regression of the logarithmic values of the last 4–5 data points. Values of C_{max} and t_{max} were noted directly from the data. The relative bioavailability was calculated from AUC values relative to the average AUC for the two oral doses, with correction for dosage differences. A formal statistical analysis was not possible because of the small number of subjects that it was possible to study.

Results

Gastrointestinal passage of the HF-capsule

The times from intake of the capsule to drug release were: stomach, 0–1.8 h; jejunum/proximal ileum, 1.3–3.8 h; colon ascendens, 4.1–7.4 h; colon transversum, 6.0–14.0 h; colon descendens, 5.3–11 h. The time from drug release to capsule excretion was at least 11.3 h (median: 17.6 h). Drug assay in saliva did not provide any evidence for drug release in the mouth during swallowing of the drug delivery device. In nine cases, ipsapirone was detected in the plasma prior to release of the capsule, and typical drug effects were reported in the interval between capsule intake and drug release. This indicated premature release of the drug, and these trials were repeated.

Individual X-ray doses for all the periods ranged from 10 to 26 mSievert to the centre of the body.

Tolerability of ipsapirone

No serious adverse events occurred. The pattern of sensations caused by ipsapirone were characteristic of the drug and proved to be a reliable predictor of premature release from the HF-capsule.

Pharmacokinetics

Pharmacokinetic parameters of ipsapirone are listed in Table 1. Median plasma concentration-time curves are shown in Figures 1a and 1b. All HF-capsule trials with evidence of premature drug release were excluded from the evaluation. The doubling of the rectal 2.5 mg dose to 5 mg resulted in approximately two-fold higher AUC and C_{max} values. Less than 1% of a dose was excreted unchanged in urine in any of the periods.

The relative bioavailability of ipsapirone was similar after oral administration and administration in the HF-capsule into the stomach and small intestine. However, the relative bioavailability after administration to the lower bowel was approximately double with respect to oral administration.

Discussion

Plasma concentrations of ipsapirone following the oral 5 mg dose of the hydrochloride (= 4.62 mg free base) were similar to those reported by others [4]. The relatively high bioavailability of ipsapirone from the colon or rectum compared with oral administration has also been described for gepirone, another azapirone derivative [10]. However, the amount of gepirone metabolites found and thus the absorbed fraction of the dose did not differ between application

Table 1 Pharmacokinetic parameters (median and range of $n = 4$) of ipsapirone following application to different sites in the gastrointestinal tract

Site of application	*Dose (mg)*	*AUC ($\mu g\ l^{-1}\ h$)*	F_{rel}† *(%)*	C_{max} *($\mu g\ l^{-1}$)*	t_{max} *(h)*	*Apparent* $t_{1/2,z}$ *(h)*
Oral1*	5.0 (5.0–5.3)	31 (20–67)		15 (12–23)	0.5 (0.5–0.8)	2.0 (0.7–2.0)
Oral2	5.0 (5.0–5.5)	29 (12–48)		19 (10–22)	0.8 (0.5–0.8)	1.0 (0.7–1.5)
Stomach	4.9 (4.9–5.0)	26 (25–44)	103 (79–119)	16 (12–17)	0.6 (0.5–0.8)	1.6 (0.8–2.7)
Small intestine	4.9 (4.9–4.9)	32 (20–64)	119 (87–150)	22 (12–31)	0.5 (0.3–0.5)	1.3 (1.1–1.4)
Colon ascendens	4.9 (4.9–4.9)	69 (40–145)	226 (195–359)	19 (12–29)	1.0 (0.5–3.0)	1.9 (0.7–3.0)
Colon descendens or transversum	4.9 (4.9–4.9)	63 (55–76)	248 (137–289)	21 (14–32)	0.4 (0.3–1.0)	2.1 (0.9–5.6)
Rectal1	0.9 (0.6–1.0)	n.d.	n.d.	4 (<2.4–8)	0.2 (0.2–0.2)	n.d.
Rectal2	2.2 (2.2–2.4)	36 (23–41)	242 (152–355)	18 (15–21)	0.3 (0.3–0.3)	1.8 (1.2–2.1)
Rectal3	4.7 (3.7–4.9)	70 (37–106)	201 (192–470)	29 (25–49)	0.3 (0.3–1.0)	1.7 (1.6–1.9)

*$n = 3$.
†F_{rel}, = relative bioavailability calculated as dose normalised AUC divided by mean AUC following the two oral administrations.
n.d., not determined because of assay limitation.

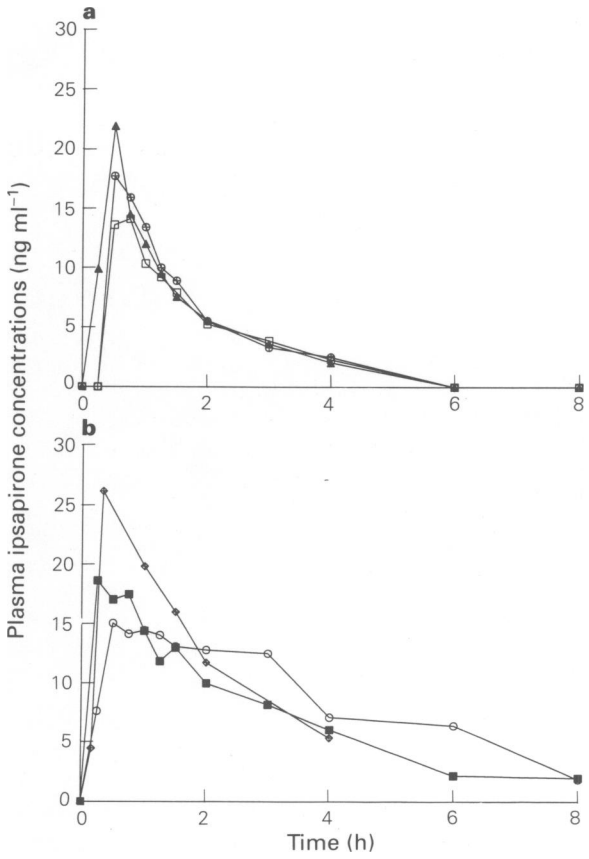

Figure 1 Median ($n = 4$) plasma concentrations of ipsapirone after administration of 5 mg ipsapirone·HCl into a) the upper (⊕ oral, □ stomach, ▲ small intestine) and b) the lower (○ colon ascendens, ■ colon descendens/ transversum, ◇ rectal) gastrointestinal tract.

sites [10]. The data indicate that oral doses of these congeners are subject to a substantial presystemic degradation which can be decreased by administration to lower gut segments.

The 2–3-fold increase in bioavailability from the colon indicates the equivalence of a 5 mg dose of ipsapirone·HCl released in the colon with a 10–15 mg dose given orally, as a linear relationship between oral dose and resulting AUC has been reported [5]. Oral doses of this size are well tolerated [5], and administration of 5 mg ipsapirone·HCl into the colon or rectum did not cause serious untoward effects. Therefore, the criteria for development of a prolonged release preparation containing 5 mg ipsaprione·HCl are fulfilled.

In this study, rectal administration and drug release to the colon gave the same results. Whether this is coincidence or a general rule merits further investigation since a simple method of estimating drug bioavailability from the colon is needed because of its importance for the development of rational prolonged-release preparations.

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