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The systemic availability of buprenorphine administered by nasal spray

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Abstract—The kinetics and systemic bioavailability of intranasally administered buprenorphine have been investigated in 9 healthy volunteers in an intranasal/intravenous cross-over study. Each subject received a nominal 0·3 mg dose of buprenorphine intranasally followed one week later by a matched dose intravenously. For the intranasal administration mean t_{max} and mean C_{max} were 30·6 min and 1·77 ng mL^{-1}, respectively. Mean intranasal bioavailability was 48·2 ± 8·3% (mean ± s.e.m.) of the intravenous value. Intranasal administration may represent a valuable new delivery route for buprenorphine.

Buprenorphine is a μ-partial agonist opioid analgesic recommended for the treatment of moderate to severe pain. In addition to a parenteral formulation the drug is available in a sublingual tablet form. The efficacy of the sublingual route is attributable to the avoidance of so called "first pass" metabolism normally associated with oral opioid therapy. In addition to the established efficacy of sublingual buprenorphine, the pharmacokinetics have also been extensively studied (Bullingham et al 1981, 1982).

Though sublingual buprenorphine has attributes of convenience, there are occasions where this route may be inappropriate. The speed of delivery is much slower than that after injection and for this reason it is inappropriate for severe acutely presenting pain. In this situation it is preferable to relieve pain with the parenteral form initially and then maintain analgesia sublingually. Also, the sublingual formulation may be unsuitable in some elderly patients, infants, patients with dry oral mucous membranes, false teeth etc.

As buprenorphine is a highly lipophilic agent, the drug might be efficiently and speedily absorbed through the richly vascularized nasal mucosa, which was considered worth investigating. Furthermore, administration via the nasal cavity in the patients described earlier, might be both more appropriate and more convenient, since an intranasal spray can be easy, quick and hygienic, as well as possibly reducing the need for other routes to be used. The work of Hussan et al (1984) showed that in rats the bioavailability of intranasally administered buprenorphine was high, but no clinical studies have been reported. Our aim was to investigate in volunteers the bioavailability of buprenorphine administered intranasally as an aqueous spray.

Materials and methods

Nine healthy volunteers (4 male, 5 female) were used in an intranasal/intravenous "cross-over" design, starting with the intranasal route and followed one week later by the intravenous route. Demographic data and doses are shown in Table 1. Normal electrolyte status, renal function and liver parameters were confirmed by blood analyses before both parts of the study. The volunteers did not show any sign of upper airways infections and their mucous membranes were examined before and after the intranasal part of the study by an ENT-specialist. The volunteers received no medication in the week before the study.

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Table 1. Demographic data and dosages given.

Subject no.	Sex	Age (years)	Weight (kg)	Height (cm)	Buprenorphine dose (mg)	
					Intranasal	Intravenous
1	M	44	75	182	0·2816	0·28
2	M	24	92	175	0·3054	0·31
3	F	20	56	165	0·2392	0·24
4	M	21	75	182	0·2856	0·29
5	F	24	54	170	0·3084	0·31
6	M	25	82	195	0·2486	0·25
7	F	26	70	172	0·3258	
8	F	18	53	162	0·3146	
9	F	24	54	170	0·2292	

The work was approved by the Ethics Committee of Copenhagen and the use of buprenorphine intranasally was authorized by the Danish Health Authority. Informed consent was obtained from all volunteers.

The spray-device and the buprenorphine-spray solution

A Pfeiffer atomizing pump (Fels & Gay 1982; Fries & Jeckle 1983) operated manually and which delivers a volume of 0·05 mL per stroke was used. The buprenorphine-spray solution was made by dissolving buprenorphine hydrochloride in 5% dextrose to a concentration of 2 mg mL^{-1} giving a delivery of 0·10 mg per pump stroke. The solution was adjusted to pH5 and the spray pumps were filled by the Pharmacy Department, Bispebjerg Hospital, Copenhagen. The pumps were prepared immediately before use.

Procedure

A centrally placed intravenous (i.v.) catheter for blood sampling was introduced through a cubital vein. In the intravenous phase of the study, the i.v. injection of buprenorphine was given in the uncatheterized arm. The intranasal doses were administered by the same person who was acquainted with the spray device. Three 0·05 mL strokes were given in the same side of the nose, i.e. the side where the volunteer subjectively felt that he/she had the best airflow. The volunteers were asked not to inhale while the spray was administered. The 3 spray-strokes (0·15 mL) were aimed to administer a nominal dose of 0·3 mg buprenorphine. The spray-bottles were weighed by a precision balance weight (Mettler) immediately before and after the spray procedure to determine the exact doses given. One week later the volunteers received the same dose intravenously as given intranasally. Blood samples were collected before (= 0) and 1, 3, 5, 10, 15, 20, 40, 60, 90, 120, 150, 180, 240, 360, 480, 720 min (12 h) and 1440 min (24 h) after the intranasal or intravenous drug administration. Blood samples were taken in heparinized polypropylene tubes, centrifuged and the plasma separated at room temperature (20°C).

Plasma was stored at −20°C in polypropylene tubes until required for analysis.

Analytical procedures and calculations

Buprenorphine in plasma was measured by a specific radioim-

Table 2. Areas under the curves (AUC_{0-720}), values of C_{max} and t_{max} and the relative systemic availability for intranasal compared with intravenous buprenorphine.

Subject no	Dose mg	Intranasal C_{max} ng mL^{-1}	Intranasal t_{max} min	Intranasal AUC_{0-720} ng·min mL^{-1}	Intravenous C_{max} ng mL^{-1}	Intravenous AUC_{0-720} ng min mL^{-1}	$\frac{AUC_{0-720\ i.n.}}{AUC_{0-720\ i.v.}}$
1	0·28	0·67	60·0	178·2	39·99	539·2	0·330
2	0·31	0·64	40·0	155·2	30·00	458·8	0·339
3	0·24	0·67	60·0	153·4	16·82	336·1	0·456
4	0·29	2·00	15·0	259·7	27·84	480·9	0·540
5	0·31	4·78	10·0	499·5	72·12	577·6	0·865
6	0·25	2·54	15·0	299·3	178·96	748·9	0·360
7	0·33	1·92	20·0	360·1			
8	0·31	0·76	40·0	220·2			
9	0·23	1·93	15·0	314·7			
Mean ± s.e.m.		1·77 ± 0·45	30·6 ± 6·6	271·2 ± 37·5	60·96 ± 24·83	523·6 ± 56·3	0·482 ± 0·083

Table 3. Mean plasma concentrations (±s.e.m.) after intranasal or intravenous administration of buprenorphine.

Time after admin (min)	Mean plasma conc ± s.e.m. Intranasal route (n = 9)	Intravenous route (n = 6)
1	0·16 ± 0·09	60·70 ± 22·09
3	0·49 ± 0·25	12·92 ± 1·35
5	0·76 ± 0·28	10·50 ± 1·13
10	1·63 ± 0·73	7·11 ± 2·46
15	1·65 ± 0·55	3·27 ± 0·33
20	1·49 ± 0·45	2·79 ± 0·25
40	1·19 ± 0·22	1·59 ± 0·13
60	1·08 ± 0·17	1·24 ± 0·08
90	0·80 ± 0·09	0·87 ± 0·10
120	0·62 ± 0·06	0·63 ± 0·06
150	0·51 ± 0·03	0·56 ± 0·04
180	0·44 ± 0·03	0·45 ± 0·04
240	0·34 ± 0·03	0·34 ± 0·03
360	0·23 ± 0·01	0·28 ± 0·02
480	0·22 ± 0·02	0·26 ± 0·02
720	0·17 ± 0·03	0·24 ± 0·02
1440	0·17 ± 0·02	0·19 ± 0·01

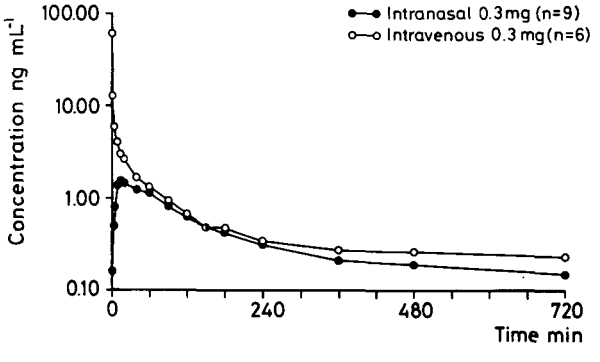

FIG. 1. Plasma concentrations of buprenorphine after intranasal administration (n = 9) and intravenous (n = 6) administration (Mean values).

munoassay procedure (Bartlett et al 1980; Hand et al 1986). All samples were analysed in duplicate.

Time to maximum plasma concentration (t_{max}) and peak plasma concentration (C_{max}) were determined from the individual volunteer plasma concentration data. The areas under the curves (AUC) were determined by a trapezoidal analysis comparing the values up to 12 h. The relative bioavailability of the intranasal dose for a subject was calculated by dividing the $AUC_{0-720\ i.n.}$ by the $AUC_{0-720\ i.v.}$

Results

Nine volunteers participated in the intranasal study, but only six continued one week later with the intravenous study. Of the three who did not continue two were excluded from the intravenous study because of earlier side effects (mainly nausea and sedation) and one because of practical difficulties in taking the blood samples.

Individual data for t_{max}, C_{max} and AUC_{0-720} are shown in Table 2 together with the relative bioavailability of the intranasal dose compared with the equivalent intravenous dose. The mean intranasal bioavailability was 48·2 ± 8·3% (mean ± s.e.m.).

Mean plasma buprenorphine concentrations after the intranasal (n = 9) and its intravenous (n = 6) administration are shown in Table 3. The corresponding curves are shown in Fig. 1.

Discussion

Recent investigations have demonstrated that the nasal mucosa can be a suitable site for drug administration (Chien 1985). The advantages of delivering drugs intranasally can be summarized as: 1) avoidance of "first-pass" metabolism, e.g. by gut wall, gut microflora or liver as may occur after oral administration, 2) the rich vascularized microvillus structure of the nasal mucosa offers an ideal absorption site for systemically active drugs and 3) the kinetics of delivery by intranasal administration are for some agents comparable to those offered after parenteral administration.

Various devices are available for delivering drugs into the nasal cavity, e.g. mechanical spray, nose drops, aerosol spray. We have used a metered dose spray operated mechanically and delivering a predetermined volume of 0·05 mL (Pfeiffer). The device consists of a piston pump and a push button which contains a twirl chamber and a nozzle. Compared with other spray devices this pump has shown a satisfactory and reproducible dosing accuracy of within a standard deviation of 10% of the intended dose (Fries & Jekle 1983) an accuracy not obtained in the present study, in part probably because aqueous dextrose was used as solution medium. Dextrose may crystallize in the nozzle or the pump cylinder and thereby change the volume given. The use of isotonic saline may solve this problem. However, according to the British Pharmaceutical Codex (1973) between 75 and 125% of the declared amount of drug has to be

delivered to the patient and this demand was fulfilled with the device used.

As the intention was to study absorption in the nasal cavity, the volunteers were asked not to inhale whilst being dosed to avoid significant aspiration of drug into the pharyngeal, laryngeal and tracheal regions. It is also feasible that some of the drug delivered intranasally may have entered the digestive tract by mucociliary clearance to be largely inactivated by first pass metabolism. From the intranasal t_{max}, the drug is rapidly absorbed from the intranasal mucosa thereby avoiding most such losses, although it is probably impossible to eliminate them. This may account for some of the variations in the amount of drug absorbed seen in this study. Individual variations in the nasal mucosa and/or nasal cavity anatomy may contribute to variability, as may the size of droplets given by the spray. The pharmacokinetics after intranasal buprenorphine were similar in profile to those achieved after intramuscular administration (Bullingham et al 1980) rather than to those after sublingual administration (Bullingham et al 1982). The mean t_{max} after the intranasal administration was about 30 min compared with average peak plasma concentrations in 5–10 min after intramuscular injection and a t_{max} of about 200 min after sublingual administration. The mean, within-patient relative systemic bioavailability after an intranasal dose averaged 48·2%, varying from 33·0% to 86·5%. As calculated from the mean AUC of each group this was 52%. The corresponding values for the intramuscular and sublingual administration according to Bullingham et al (1980, 1981, 1982) were 40–90% and 31–57·7%, respectively. Although 24 h blood samples were taken, the AUC values were only calculated to 12 h as plasma concentrations after this time were barely above the detection limit of the assay and thus unreliable as would have been an extrapolation of the curves to yield $AUC_{0-\infty}$ values. In practice, the comparison of $AUC_{0-12\,h}$ data were considered well justified.

In conclusion, intranasal administration of buprenorphine may represent a new delivery route approaching the effectiveness of the intramuscular route but without the problems associated with invasive techniques.

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Decreased 5-hydroxytryptamine turnover in striatum and other brain regions after administration of 5-methoxy-3-(di-n-propylamino)-chroman to rats

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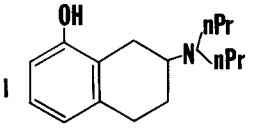
Abstract—5-Methoxy-3-(di-n-propylamino)chroman (5-MeO-DPAC) caused a dose-dependent decrease in the accumulation of 5-hydroxytryptophan after decarboxylase inhibition in rat striatum, hippocampus and frontal cortex. The decreased 5-hydroxytryptamine (5-HT) turnover may have resulted from activation of 5-HT receptors on cell bodies of 5-HT neurons that project to the striatum and other brain regions, since 5-MeO-DPAC had earlier been reported to lack affinity for striatal binding sites.

5-Methoxy-3-(di-n-propylamino)chroman (5-MeO-DPAC, II) is a structural analogue of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, I) and shares with the latter compound a high and selective affinity for $5\text{-}HT_{1A}$-binding sites (Cossery et al 1987). When tritiated 5-MeO-DPAC was used as a radioligand, it labelled sites in hippocampal and cortical membranes from rat brain apparently identical to those labelled by tritiated 8-OH-DPAT. In contrast to tritiated 8-OH-DPAT, tritiated 5-MeO-DPAC did not bind to striatal membranes. 8-OH-DPAT, like other 5-hydroxytryptamine (5-HT) agonists, decreases 5-HT turnover in rat brain (Arvidsson et al 1981; Hjorth et al 1982; Fuller 1985). 8-OH-DPAT has been shown to decrease 5-HT turnover in the striatum just as in hippocampus and other brain regions in rats (Hjorth et al 1982). The current study was undertaken to see if 5-MeO-DPAC affected 5-HT turnover in the striatum, where binding sites for it were not present, and in other brain regions.



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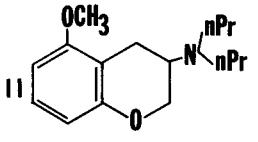
8-OH-DPAT



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5-MEO-DPAC

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