J. Pharm. Pharmac., 1973, **25**, 376–381 *Received December* 4, 1972

Serum and blood concentration of sodium cephalexin in man given single intramuscular and intravenous injections

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Healthy volunteers were given a single intramuscular (i.m.) injection of a solution of 1 g, 500 or 250 mg sodium cephalexin or an intravenous (i.v.) injection of 1 g. Following i.m. injection, mean peak serum levels were estimated by computer analysis to be 18·3, 17·9 and 8·2 μg ml^{-1} respectively. The mean serum level 15 min after i.v. injection was 52·5 μg ml^{-1}. The rate of recovery of cephalexin in the urine after i.m. injection was slower than after both i.v. injection and oral administration. Concentrations of cephalexin in the urine reached a higher maximum after i.v. than after i.m. injection, but were maintained for a shorter time. Analysis of the data after i.m. injection suggests the occurrence of a depot-like effect.

Cephalexin, formulated for injection, either as an aqueous solution or an aqueous suspension, has been given subcutaneously, intramuscularly, intravenously and intraperitoneally to animals (Welles, Froman & others, 1968; Foord, O'Callaghan & others, 1969). Injections to man have seldom been reported and these were given intravenously, either as a constant infusion (0·5 g h^{-1}) or as a 500 mg bolus (Kirby, de Maine & Serrill, 1971).

Whether cephalexin could be usefully employed by parenteral routes has now been examined using single 1 g doses given either intramuscularly or as an intravenous bolus injection or as single intramuscular doses of 1 g, 500 and 250 mg to healthy volunteers. The results are compared with a similar study of oral 1 g doses previously reported by Gower & Dash (1969).

METHODS

Intramuscular injection

Seven volunteers each received 1 g of cephalexin (1·12 g sodium salt in 3·2 ml water, freshly prepared) by injection (21G × 1½″ needle) into the thigh or buttock.

Urine was voided immediately before injection. Thereafter urine was collected as indicated in Table 3 and venous blood samples as in Table 1. Eight different volunteers each received 500 mg and two further volunteers 250 mg of the same preparation intramuscularly.

Intravenous injection

Each of six volunteers was given a bolus injection of 1 g cephalexin into the median cubital vein over 5 min as sodium cephalexin (1·12 g) dissolved in 3·2 ml of water or in 10 ml of physiological saline. Urine and blood samples were collected as shown in the

Tables. At least the first two samples of venous blood were obtained from the contralateral arm.

All blood samples were allowed to clot, and after centrifugation the serum was stored at −20°. Aliquots of urine, after measurement of volumes, were stored without preservative at −20°. Assays were carried out in batches by agar diffusion using *Sarcina lutea* ACTC 8340 (laboratory reference 400E) for the samples from the 1 g study, and *Bacillus subtilis* ACTC 6633 for the samples from the 500 mg and 250 mg studies. The limit of sensitivity was 0·3 μg ml^{-1}.

There was an interval of at least two weeks between the 1 g intramuscular and intravenous studies for those individuals who participated in both.

RESULTS

Intramuscular injection

Serum levels are given in Table 1. The highest mean concentration after 1 g was

Table 1. *Mean serum concentrations, with ranges in parentheses, following cephalexin given by various routes.*

Time after injection (h)	Intramuscularly 250 mg (μg ml^{-1})	Intramuscularly 500 mg (μg ml^{-1})	Intramuscularly 1 g (μg ml^{-1})	Intravenously 1 g (μg ml^{-1})	Orally* 1 g (μg ml^{-1})
¼	6·7 (5·3–8·1)	—	—	52·5 (43·6–66·0)	—
½	8·1 (8·0–8·1)	16·6 (9·9–25·4)	12·8 (1·8–23·7)	32·5 (25·9–38·5)	
¾	8·1 (8·0–8·1)	—	—	—	—
1	7·4 (7·2–7·5)	13·3 (8·8–18·5)	17·0 (9·0–26·2)	16·7 (15·5–18·3)	31·6 (26·7–35·6)
1½	—	9·4 (6·2–12·7)	—	—	—
2	4·3 (3·6–3·9)	6·0 (4·0–8·6)	13·9 (11·8–17·8)	7·3 (5·6–9·3)	15·9 (12·7–25·0)
3	3·6 (3·3–3·9)	3·5 (2·7–4·5)	—	—	—
4	—	—	6·0 (3·3–8·0)	1·7 (1·2–2·2)	2·3 (1·1–3·3)
5	—	2·9 (2·3–3·5)	—	—	—
6	—	—	2·4 (0·9–3·9)	0·3 (<0·3–0·4)	0·5 (0·5–0·6)

* Fasting subjects.

17 μg ml^{-1} and occurred at 1 h. The serum half-lives were calculated for each individual by the method of least squares. Values ranged from 66 to 140 min with a mean of 99 min.

The highest mean concentrations observed after 500 mg and 250 mg were 16·6 and 8·1 μg ml^{-1} respectively and occurred at ½ and ¾ h after injection.

Data were analysed by the method of O'Callaghan, Toothill & Robinson (1971). This method assumes the relation between serum level and time after administration can be expressed by a standard exponential pharmacokinetic formula. This is fitted, by means of a computer, to the levels for each individual and from the curve it is possible to estimate, amongst other parameters, the actual peak serum concentration reached

Table 2. *Mean values, with ranges in parentheses, after analysis of the data obtained after intramuscular injection of sodium cephalexin (O'Callaghan & others, 1971).*

Intramuscular dose	Peak serum concentration (μg ml^{-1})	Time of peak serum level (min)	Time of first serum level (min)	Area under curve
250 mg	8·2 (8·1–8·2)	33·5 (33·1–33·9)	4·1 (0–8·2)	24·1 (21·4–26·7)
500 mg	17·9 (10·5–27·7)	25·9 (10·6–38·4)	8·5 (0–24·9)	33·4 (22·2–44·2)
1 g	18·3 (11·7–26·9)	67·7 (43·1–103·3)	10·8 (0–25·8)	59·2 (50·5–81·3)

in vivo, the time at which this peak occurred and the time the drug first entered the blood. The results are shown in Table 2.

The computer also calculates the area under the serum level curve and the excretion rate. The apparent volume of distribution after 1 g of the drug was then estimated for each individual by employing the product of the area under the curve and excretion rate as denominator and the dose of drug as the numerator. The mean value of the apparent volume of distribution so calculated was 37 litres, (range 26 to 53 litres). The renal clearance rate, reckoned as the quotient of the amount of drug recovered in the urine divided by the calculated area under serum level curve, had a mean value of 260 (range 160–410 ml min^{-1}) and is similar to the 376 ml min^{-1} found in a single volunteer, using a different method, after oral cephalexin (Gower & Dash, 1969).

Urinary concentrations and recoveries are recorded in Table 3. The highest mean concentration after 1 g (2757 μg ml^{-1}) was found in the 2-4 h period, whereas after 500 mg the highest mean concentration (2305 μg ml^{-1}) was found in the first 2 h.

The mean total recoveries over the first 6 and for the 24 h are given in Table 4. There was no significant difference between the amounts excreted in the first and second 2 h collection periods.

Table 3. *Mean urine concentrations, with ranges in parentheses, following cephalexin given by various routes.*

Collection period (h)	Intramuscularly 500 mg (μg ml^{-1})	Intramuscularly 1 g (μg ml^{-1})	Intravenously 1 g (μg ml^{-1})	Orally* 1 g (μg ml^{-1})
0–2	2305 (700–5600)	1973 (225–3820)	4980 (3510–7550)	7318 (5280–8985)
2–4	1191 (270–2037)	2757 (1580–5008)	1319 (922–2021)	3582 (1095–7055)
4–6	339 (175–582)	1439 (408–2633)	314 (136–526)	1448 (170–4395)
6–12	45 (7·4–93·4)	342 (4–1018)	58† (25–74)	—
12–24	5·7 (<1·2–24)	35 (4–117)	2·5† (0–7)	—

* Fasting subjects

† 5 volunteers

Table 4. *Mean recoveries of cephalexin, with ranges in parentheses, following cephalexin given by various routes.*

	Collection period (h)	Intramuscularly 250 mg (%)	500 mg (%)	1 g (%)	Intravenously 1 g (%)	Orally* 1 g (%)
	0–2	—	54 (37·1–69·6)	37 (2·3–62·1)	62 (45·4–86·8)	62 (53·0–71·5)
	2–4	—	24 (18·6–31·0)	30 (16·1–55·4)	13 (8·0–24·3)	22 (8·5–35·0)
	4–6	—	7 (1·5–10·7)	13 (8·6–15·8)	3·1 (2·0–4·0)	10 (3·6–40·5)
TOTAL	0–6	—	85 (76·9–98·4)	80 (48·2–126·0)	78·1 (55·5–101·7)	94·7 (79·6–111·3
	6–12	—	3·0 (1·7–4·6)	6·7 (0·3–11·7)	2·0 (1·1–2·6)	—
	12–24	—	0·5 (0·1–2·9)	3·6 (0·02–13·0)	0·2 (0 –0·3)	
TOTAL	0–24	68·4 (67·2–72·0)	88·5 (79·8–104·9)	90·3 (63·5–126·4)	77·1† (58·8–103·8)	—

* Fasting subjects

† 5 volunteers only

Intravenous injection

Serum levels. Table 1 gives the mean and ranges of the serum levels at each time interval after 1 g intravenously. The highest mean concentration was 52·5 μg ml^{-1} and occurred $\frac{1}{4}$ h after injection but by 6 h the concentration was at the limit of the assay (0·3 μg ml^{-1}). The mean serum half-life was 48 min (range 43 to 52 min).

Urinary concentrations and recoveries. The mean urine concentrations and recoveries for each collection period following 1 g intravenous injection are shown in Tables 3 and 4 respectively. Maximum urine concentrations of cephalexin occurred in all volunteers in the first 2 h after injection (mean value 4980 μg ml^{-1}) when 62% of the dose was excreted (Table 4). 78·1% of the dose was recovered from the urine in the first 6 h. A further 2% was generally recovered in the next 18 h.

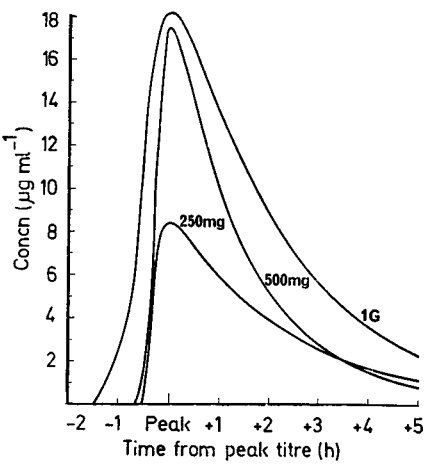

FIG. 1. Computed serum concentrations after 250, 500 mg and 1 g doses of sodium cephalexin intramuscularly.

DISCUSSION

The peak serum concentration after a single oral dose of cephalexin acid is closely proportional to the dose, at least up to 1 g (Griffith & Black, 1968; Muggleton, O'Callaghan & others, 1968). However, this relation does not appear to be maintained with intramuscular sodium cephalexin. Mean peak serum concentrations of 18·3, 17·9 and 8·2 μg ml^{-1} were found after 1 g, 500 and 250 mg doses respectively. The computer derived serum level curves for these three doses are shown in Fig. 1. The computer-calculated area under the serum level curves was approximately doubled between the 500 mg and 1 g doses, 33·4 and 59·2 respectively (Table 2). With the 250 mg dose, the area under the curve was relatively high (24·1), even though the total recovery of cephalexin in the urine was relatively low at this dose, 68·4 compared with 88·5 and 90·3% after 500 mg and 1 g respectively (Table 4). The highest recovery of cephalexin in the urine was obtained in the oral study (Table 4). The reasons for these differences are not clear.

The mean apparent volume of distribution after intramuscular injection (37 litres) is greatly in excess both of the 10 to 16 litres (mean 12 litres) after oral administration (unpublished data) using the same method of calculation and of the 15 litres at the steady state with an intravenous infusion reported by Kirby & others (1971).

The mean serum half-life of 48 min after intravenous injection is comparable with that of 49·5 min found after oral administration of 1 g cephalexin to fasting volunteers (Gower & Dash, 1969), but was longer than the 36·6 min reported after attainment of a steady state with a constant intravenous infusion (Kirby & others, 1971). The mean apparent serum half-life of 99 min after intramuscular injection suggests that absorption may have been still occurring some hours after injection and probably represents the rate of absorption from the muscle rather than the rate of excretion.

It is probable that a local depot effect occurs after the intramuscular injection. A possible explanation is that the tissue fluid of muscle has such a strong buffering potential that the pH of the injection, which normally lies between 9·0 and 10·0 (G. D. Andrews & T. Wallis, personal communication) is reduced to the extent which results in some precipitation of free acid. However, animal experiments with the salt had not indicated a depot effect (P. W. Muggleton, personal communication), nor have we observed precipitation when sodium cephalexin was added *in vitro* to human plasma.

Comparison of the urinary concentrations after intravenous, intramuscular and oral administration has shown that therapeutically useful levels are present up to at least 6 h after a single dose. The higher concentrations in the oral study (Gower & Dash, 1969) were likely to be due to restrictions in fluid intake from 12 h before until 6 h after administration.

Conclusions

The indications for cephalexin by the intramuscular route may be limited to those patients who cannot take drugs orally, or to conditions in which advantage can be taken of the presumed depot effect, because cephalexin by mouth gives good serum levels and is generally well tolerated even in high dosage (Dash, Foord & others, 1971).

Cephalexin by the intravenous route may be useful clinically: it is not metabolized, has an apparent low toxicity (Dash & others, 1971) and does not seem to be nephro-

toxic (Eykyn, 1971). It shows satisfactory stability with commonly used intravenous fluids such as 5% dextrose or normal saline, at least up to concentrations of 30 mg ml^{-1} for up to 24 h at room temperature (G. D. Andrews & T. Wallis, personal communication). Higher serum levels may safely be obtained by larger intravenous doses even without probenecid: a serum concentration of 27 $\mu g\ ml^{-1}$ was maintained at the steady state with an infusion rate of 0·5 g h^{-1} (Kirby & others, 1971). Even if such a dosage was given for some days the sodium ion content (2·9 mequiv g^{-1}) is unlikely to give rise to electrolyte disturbances.

Finally, therapy could be continued with the same antibiotic by the oral route when the need for parenteral administration ends.

Acknowledgements

The authors thank Glaxo Laboratories Ltd, Greenford, Middlesex, who supplied the sodium cephalexin, Miss Monica Marshall and Miss Susan Kirby for technical assistance and Mrs. Susan Howe for secretarial services.

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