Epidural and intramuscular pethidine — a pharmacokinetic study

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Summary

Epidural preservative-free pethidine hydrochloride 0,75 mg/kg is rapidly absorbed into the blood. At 1,5 mg/kg the plasma levels reached are similar to those achieved by intramuscular preservative-free pethidine hydrochloride, as is the time course. Plasma levels fall more rapidly after epidural pethidine. Since the plasma levels lag behind the analgesic effects, they are unlikely to be of importance as regards clinical analgesia.

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Epidural opiates such as pethidine have been shown to provide effective postoperative analgesia,[1,2] their site of action being the substantia gelatinosa of the spinal cord.[3,4]

The epidural space contains many lymphatics and venous plexuses,[5,6] and systemic absorption can therefore be rapid; as doses of pethidine equal to intramuscular doses have been used epidurally,[2] blood levels may play a part in their action.

Serial measurements of CSF pethidine levels in patients undergoing routine operations pose ethical problems, but plasma samples are easily and painlessly taken. It was therefore decided to compare plasma levels of pethidine after epidural injection of 0,75 mg/kg and intramuscular injection of 1,5 mg/kg. These were the doses used in a previous study[1] showing that epidural pethidine provided superior quality analgesia but was not associated with an increase in the incidence of side-effects. This study would indicate to what extent absorption and transport via the blood influenced the actions of epidural pethidine.

Methods

Consent of the hospital ethical committee was obtained, and the patients gave written informed consent. They were all fit, non-

obese, gynaecological or orthopaedic patients in ASA (American Society of Anesthetists) grades 1 or 2, and none was on any medication. Eleven patients received intramuscular and 10 epidural pethidine.

Premedication was with oral diazepam 10 mg 2 hours preoperatively. Two patients in the epidural group received metoclopramide 10 mg intravenously for nausea during the trial. Bupivacaine 0,5% (plain) was used for all skin infiltration. The intravenous fluid lines were inserted into the feet. Blood sample lines were inserted into the cubital fossae of all patients, Teflon catheters being used. Three-way taps allowed all the samples to be taken from the same vein.

The patients in the intramuscular group were operated on under brachial plexus block with bupivacaine 0,5%, tourniquets being used. Intravenous diazepam was used in 7 cases for mild sedation. Patients received no fluids via their intravenous lines until all blood samples had been taken. Preservative-free pethidine hydrochloride 1,5 mg/kg was given by deep intramuscular injection into the quadratus femoris muscle on the opposite side to the intravenous line. Blood samples were taken during the operation, one before the intramuscular pethidine and thereafter every 5 minutes for 45 minutes.

In the patients in the epidural group the epidural catheters were placed by routine methods, bupivacaine 0,5% being used for all skin infiltration. The intravenous lines were not inserted into the same arm as the blood sample lines. No intravenous fluids were given until all blood samples had been taken. Preservative-free pethidine hydrochloride 0,75 mg/kg in 10 ml normal saline was then introduced down the catheter. Blood samples were taken before and during the operation. Thereafter bupivacaine 0,5% was given through the catheter and a satisfactory block elicited. If the block proved unacceptable, the patient was taken out of the trial.

The blood samples were taken into heparinized glass test tubes and centrifuged immediately, and the plasma was decanted into glass test tubes and stored in the deep-freeze at 0°C until analysed. The plasma extract was passed through a Philips GCV gas chromatograph using a 1,1 metre glass column of 2% Carbowax 20M + 3% KOH on Chromasorb W-AW 80/100 at an oven temperature of 200°C according to the method of Tucker.[7] Samples were assayed in duplicate wherever possible.

Results

The two groups were well matched for age and weight (Table I). Males predominated 9 to 2 in the intramuscular group, while there were 5 males and 5 females in the epidural group. Tables II and III show the range in values and standard deviations; these show great variability, which was marked in both groups. The epidural group definitely received their pethidine into the epidural space, as operation was later undertaken with the catheter *in situ;* similarly, the intramuscular group received truly intramuscular injections.

Fig. 1 shows the mean plasma levels in the two groups. The initial values are remarkably close, both rising at similar rates to peak in 25 minutes at 110 ng/ml for the intramuscular group and 98 ng/ml for the epidural group. Up to this time there was no statistical difference between the groups ($P > 0,05$). Thereafter the values in the epidural group rapidly dropped to a mean of 68

TABLE I. THE PATIENTS

	Intramuscular group				Epidural group			
Patient No.	Age (yrs)	Weight (kg)	Sex	ASA rating	Age (yrs)	Weight (kg)	Sex	ASA rating
1	22	75	M	1	33	80	M	1
2	21	75	M	1	49	75	F	2
3	48	52	M	1	36	44	F	1
4	14	50	M	1	20	79	M	1
5	20	50	M	1	49	60	F	2
6	22	53	M	1	43	59	M	2
7	27	72	M	1	28	50	F	1
8	59	88	M	1	16	50	M	1
9	29	54	F	1	44	64	M	1
10	54	60	F	1	28	56	F	1
11	38	80	M	1				
Mean	32,2	64,4			34,6	61,7		

TABLE II. PLASMA PETHIDINE LEVELS (ng/ml) IN THE INTRAMUSCULAR GROUP

Patient No.	0	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min
1	0	25	61,5	28,5	29,5	13	11,7	11	7	34,5
2	<12,5	31	20	36	45	67,5	64,5	89	92	76
3	0	8,5	40	87	97	73	36	—	31	—
4	0	—	187	86	52	100	164	64	133	96
5	0	50	72	104	152	177	146	146	143	137
6	0	11,5	90	158	158	158	190	162	114	197
7	0	50	62	64	64	124	118	102	66	41
8	0	0	8,5	32	54	104	108	158	60	143
9	0	35	185	240	90	187	170	147	216	94
10	0	21	48	56	61	67	63	54	51	50
11	0	47	82	157	147	147	142	139	136	133
Mean	0	27,9	77,7	95,3	86	110,6	110	107	95	100
Range		0-50	8,5-187	28,5-240	29,5-158	13-187	11,7-190	11-162	7-216	34,5-197
SD		17,8	58,8	65,8	46,4	53,7	58,9	51,6	60,2	52,2

TABLE III. PLASMA PETHIDINE LEVELS (ng/ml) IN THE EPIDURAL GROUP

Patient No.	0	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min
1	0	61	70	88	102	81	84	76	74	82
2	0	21,5	68	120	121	84	82	71	69	46
3	0	18	30	25	25	22,5	23	21	21	18
4	12,5	17	20,5	45	73	48	38	37	34	32
5	0	6	8,5	23	58	52	30	43	54	59
6	0	75	156	165	138	129	119	102	97	96
7	0	12	12,5	30	32	211	92	61	166	92
8	0	36	153	153	226	203	189	124	156	137
9	0	16	36	61	66	104	63	61	57	43
10	0	0	18	27	28	47	53	80	70	42
Mean	0	26,2	57,2	73,7	86,9	98,1	77,3	67,6	79,8	64,7
Range		0-75	8,5-156	23-165	28-226	22,5-211	23-189	21-124	21-166	18-137
SD		24,1	55,4	54,7	62,4	60,5	49,4	30,5	47,7	36,3

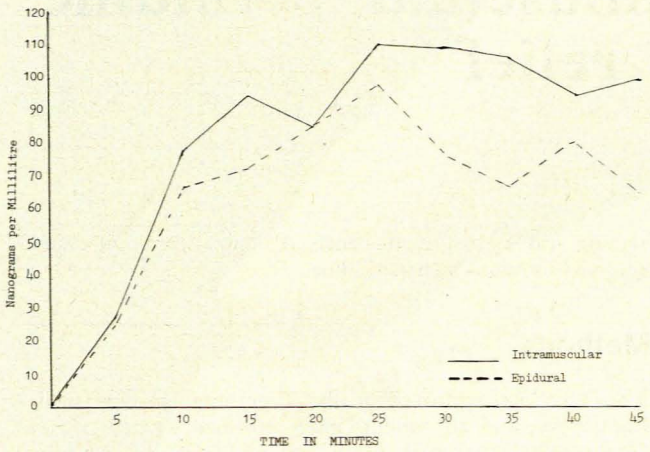

Fig. 1. Mean plasma pethidine levels. At 35 and 45 minutes these levels are significantly different ($P < 0,05$).

ng/ml at 35 minutes, while those in the intramuscular group fell more slowly to 100 ng/ml at 45 minutes. The differences at 35 and 45 minutes were significant at a confidence level of 95% ($P < 0,05$).

Discussion

Intramuscular pethidine has long been used for postoperative pain relief, but like all intramuscular analgesics its efficacy is variable,[8,9] probably because varying rates of absorption lead to differences in plasma levels.[10-12] This variability is well shown in this study. The range of blood levels reached and the different times for peak levels are marked. Intramuscular pethidine is said to reach peak plasma levels at 60 minutes,[12-14] but the peak in this study was much earlier (25 minutes) and the levels fell slowly for the remainder of the time. The fact that these were all fit patients whose cardiovascular homeostasis was unaffected by operation or pain is likely to be the reason for the early peak levels.

It is reported that plasma pethidine levels of 200 ng/ml are needed for analgesia.[2,11,12] The mean peak level in the intramuscular group was only half this and no individual patient surpassed this level. This supports the clinical impression that intramuscular pethidine does not provide powerful analgesia at 1,5 mg/kg.

The vascularity[5,6] of the epidural space suggests rapid absorption. This has been shown with local anaesthetics.[15] The plasma levels in the epidural group show that the absorption rate was close to that of the intramuscular group, although the patients received only half the dose. However, the more rapid fall in plasma levels in the patients who received epidural pethidine probably reflects the smaller dose, producing less of a reservoir. The values up to 25 minutes are close to those reported by Cousins *et al.*,[2] who used double the dose. In that study the peak value was maintained to 45 minutes, probably because the dose of 100 mg provided a reservoir; furthermore, the pethidine levels in Cousins *et al.*'s study were measured postoperatively and those in the present study pre- and intra-operatively, so perfusion and absorption rates may be different. As with intramuscular pethidine, the variation in levels reached is very large. The highest plasma level reached was just on the analgesic level, but the rapid fall-off makes it unlikely that it would be significant in pain relief.

The analgesia produced by epidural pethidine takes effect in 5 - 10 minutes[1,16] when the plasma levels are low. Analgesia at this stage is therefore probably due to rapid spread in the CSF, resulting in analgesic levels in the CSF at this time.[2] However, with the plasma concentrations in both groups reaching similar levels at 25 minutes, it is surprising that epidural pethidine does not lead to the central depression associated with intramuscular pethidine. Reports all stress the lack of sensory clouding.[1,2,11,17] Early drowsiness, with onset at 5 minutes and wearing off again at 30 minutes, has been reported.[1] This is not due to spread in the blood as the patients are recovering at the time the plasma levels peak.

The plasma levels achieved suggest that blood spread may play a part in the clinical effect of epidural pethidine but that this is less significant than spread in the CSF, especially with regard to analgesia.

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