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ANALGESIC EFFECT AND BIOAVAILABILITY OF ORAL KETOGAN GIVEN AS TABLETS OR MIXTURE TO PATIENTS WITH CHRONIC PAIN OF MALIGNANT ORIGIN

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Abstract

Thirteen cancer patients with moderate to severe chronic pain of malignant origin on treatment with Ketogan tablets were included in an open non-randomized cross-over study comparing the analgesic effect, side effects and serum concentrations of Ketogan tablets and mixture. The patients were six days in hospital and were dosed two days with tablets, two days with mixture and finally another two days with tablets. Recordings of pain and side effects and collection of blood samples prior to dosing and hourly thereafter until remedication were performed on the second day of each dosing period in a morning dose interval. The analgesic effect judged by visual analog score (VAS) and pain intensity differences (PID), the areas under the serum concentration time curves, and the average serum concentrations for the three groups were compared. It was not possible do detect any differences among the three groups concerning the analgesic effect, duration of analgesic effect, the serum concentrations and the side effects. The mean plasma half-life of ketobemidone was 2.74 h±0.90 (SD) and the mean relative bioavailability of the mixture was slightly above 100%. Linear regression analysis revealed a significant correlation between ketobemidone serum concentrations and analgesic effect, VAS, for tablet one and for the mixture but not for tablet two, possibly due to the fixed dosing schedule and to the positive effect of hospitalization on the pain.

Key words: Ketogan, cancer pain, ketobemidone pharmacokinetics.

A combination of ketobemidone and the spasmolytic drug A29,N,N-demethyl-3,3 diphenyl-1-methyl-allylamin, in the ratio 1:5 is in the Scandinavian countries marketed as Ketogan or Ketogin. It has been used for the treatment of severe pain for more than 30 years and is often the drug of first choice in cancer patients with chronic pain. In spite of its common use very few data are available concerning its pharmacokinetics and bioavailability. These data have recently been reviewed (3). The existing data derive from a few small investigations of patients during an uncomplicated postoperative course (1, 2, 4, 5). They demonstrated a mean serum half-life of 2.45±0.93 h (SD), and a considerable interindividual variation in bioavailability 17–62%, mean 34%±16% (SD) for ketobemidone after oral administration of 10 mg (2 tablets). Thus, Ketogan has a relatively short half-life and a moderate bioavailability after oral dosing. No data concerning analgesia are available from these investigations, and no data are available concerning the pharmacokinetics of Ketogan in cancer patients on chronic pain treatment.

With Ketogan, these patients will need a relatively large and frequent (3–4 hourly) tablet intake, which may be distressing in advanced cancer patients who have nausea and loss of appetite because of their disease and treatment (9). We therefore developed a Ketogan mixture identical to the tablets. The aim of the present study was to compare the analgesic effect, side effects and serum concentrations of ketobemidone and A29 after Ketogan tablets and Ketogan mixture in an open cross-over study of cancer patients with moderate to severve chronic pain due to their malignant disease. Moreover, we would try to correlate the serum concentrations of ketobemidone with the analgesic effect and side effects.

Material and Methods

Patients

Thirteen patients on treatment with oral Ketogan were included in the study. Patient characteristics emerge from Table 1 (patient No. 5 not shown). All patients had histo-

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Table 1

Patient characteristics

Patient No.	Sex	Age (years)	Weight (kg)	Perf. status WHO	Diagnosis	Localization of pain (cause of pain)	Dose of Ketogan (tablets per dose/No. doses per day)	Duration of treatment before study (months)
1	F	37	68	1	Cancer of the cervix uteri St. II B Relapse	Small pelvis, paravesical region	2/5–6	7
2	M	63	85	2	Prostate cancer St IV Bone metast.	Spine, shoulder, pelvis	1/4	3
3	M	51	79	2	Lung cancer WHO III Bone metast.	Right femur	3/8	1
4	M	36	72	1	Renal adeno-carc. St IV Relapse in kidney bed	Right kidney	2/4	4
6	M	60	52	2	Prostata cancer St IV Bone metast.	Left pelvis	2/5	5
7	M	72	64	2	Bladder cancer T_3 Bone + skin metast.	Left pelvis and femur	2/5	1
8	M	58	51	3	Lung cancer WHO IV Abdominal relapse	Lower abdomen	1/4	9
9	M	63	73	1	Lung cancer WHO III Bone and plexus invasion	Left shoulder	2/6	8
10	F	68	53	2	Bladder cancer T_3 Pelvic lymph nodes	Paravesical, left pelvis	2/6	1
11	M	66	74	1	Lung cancer WHO II Bone marrow carcinosis	Left pelvis and femur	2/5	1
12	M	68	71	2	Renal adeno-carc. St IV Bone and medi-tastinal metast.	Left femur	2/5–6	1
13	M	59	56	1	Prostata cancer St IV Retroperitoneal metast.	Low spine, pelvis	2/6–7	2

Table 2

Flow diagram of the investigation

	Sun.	Mon.	Tue.	Wed.	Thu.	Fri.	
Patients on treatment with Ketogan	tabl.	tabl.	mixt.	mixt.	tabl.	tabl.	Patients discharged from hospital (continuation of the Ketogan treatment)
	1 Admission to hospital. Recordings of pain and medication. Instruction of the patient	2 Evaluation of pain (VAS, PI), side effects and collection of blood samples	3	4 Evaluation of pain (VAS, PI), side effects and collection of blood samples	5	6 Evaluation of pain (VAS, PI), side effects and collection of blood samples	

logically proven and often heavily treated malignant disease in a relatively advanced stage. There were 11 men and 2 women, median age 63 years, range 36–68 years with a median performance status of 2, range 1–3, and a median weight of 72 kg, range 51–85 kg. The localization of the primary tumors was as follows: 4 patients lung, 3 prostate, 3 bladder, 2 patients with renal adenocarcinoma, and 1 cervix uteri. The median time on opiate treatment before inclusion in the study was 3 months, range 1–9 months. Converted to mg ketobemidone per 24 h the median dosage was 60 mg, range 20–120 mg.

All patients were informed in detail about the aim and design of the study before inclusion and gave their informed consent to participate. The study protocol was approved by the Ethics Committee for Copenhagen before activation.

Study design and patient evaluation

A flow diagram of the study is shown in Table 2. Patients on treatment with Ketogan tablets were chosen from our outpatient clinics. The dose of Ketogan needed by the individual patient was determined in each case through a number of outpatient visits before inclusion in the study. A fixed time interval dosing schedule was attempted in all cases. The median dose of ketobemidone was 10 mg, range 5–15 mg, the median dosing interval 4 h, range 3–6 h (Table 1). Patients were hospitalized on a Sunday afternoon. Detailed recordings of pain anamnesis, pain foci, performance status and all analgesic and non-analgesic medications were performed by the responsible investigator and a trained nurse observer who followed the patients and made all the recordings throughout the study period. On day 2—Monday—a morning dose interval was chosen. Recordings of pain and side effects were performed and venous blood samples drawn prior to dosing of Ketogan tablets and hourly thereafter until remedication. The time until remedication was determined by the fixed time interval dosing schedule, but in case of pain relapse patients were remedicated earlier. Serum was separated by centrifugation and kept frozen (−18°C) until analysis.

As in previous analgesic studies by our group (6, 7) the following evaluation program was used:

1. *Visual analog score* (VAS), a 100 mm, end-barred horizontally placed scale indicating no pain—intolerable pain in either end was used.

2. *Categorical pain intensity scale* (PI), a 4-point scale was used by the nurse observer.

3. *12-side effects* were scored at each observation time and graded 0–3 according to severity by the nurse observer. These were the following: sedation, dizziness, confusion, euphoria, depression, nausea, vomiting, sweats, hallucinations, headache, blurred vision and thirst (dry mouth).

At 24.00 h in the night between day 2 and 3 Ketogan tablets were replaced by the same dose of Ketogan mixture containing 1 mg ketobemidone and 5 mg A29 per ml. One Ketogan tablet = 5 mg ketobemidone = 5 ml mixture. On day 4, i.e. after at least 32 h of treatment with the mixture, recordings and blood samples as outlined above were repeated in a morning dose interval. At 24.00 h in the night between day 4 and 5 the treatment was crossed to Ketogan tablets. On day 6 recordings and blood samples were repeated in a morning dose interval. The patient was discharged from hospital in the same afternoon with his initial dose of Ketogan tablets, to be followed in the outpatient clinic at regular intervals.

Analysis of ketobemidone and A29

Ketobemidone. The HPLC-system used for the analysis of the serum samples consisted of a Waters 6000A pump, a Rheodyne 7125 injection valve with a precolumn instead of the sample loop (8), and a Bioanalytical Systems LC4B/17 electrochemical detector. The electrode was glassy carbon with an Ag-AgCl electrode as reference. The applied potential was 1.1V. A 2-channel BD-9 recorder (Kipp & Zonen) was connected to the detector. An HP 3390A integrator (Hewlett Packard) was used to measure peak heights. The column was a Knauer column (250×4 mm ID) packed with Spherisorb C-18 (5 μm) material.

Pre-column. The pre-column (8) was used in the backflush mode and packed with LiChroprep 40–63 μm, C-18

(Merck) and closed with 30 μm sieves. The dimensions of the column were 7×4 mm ID.

Mobile phase. The mobile phase was 0.2 M phosphate buffer (pH 6.5)–methanol (50:50) with a flow of 1.5 ml/min.

One ml serum and 50 ng of morphine (internal standard) or 75 ng of Lu 21-051 (internal standard used for samples that contained morphine) were mixed. The sample (1 ml) was injected directly on a pre-column after the pre-column was flushed with 1 ml of water.

The pre-column was again flushed with water (5 ml) before the sample was injected into the HPLC-system. A linear standard curve was obtained after analysing human blank serum spiked with ketobemidone. The limit of detection was 1 ng/ml. The within-day precision was better than 5% and the day-to-day precision better than 6.5%.

A29. The analysis of A29 was performed with the same HPCL-system as used for the analysis of ketobemidone except for the column and the mobile phase. The column used for the analysis of A29 was a Knauer column (250×4 mm ID) packed with Spherisorb Phenyl (5 μm) material. The mobile phase consisted of 0.1 M phosphate buffer (pH 6.5)–acetonitrile (50:50) with a flow rate of 1.5 ml/min.

The limit of detection was 5 ng/ml. All determinations (both ketobemidone and A29) were done in duplicate.

Data treatment

The pain intensity differences (PID) and the VAS differences were calculated by subtracting the score at each observation time from the score prior to drug administration. The area under the curve (AUC) of the PID scores, the VAS differences and the serum concentrations were calculated by the trapezoidal rule.

Average serum concentration were calculated by dividing the AUC for the serum concentrations by the length of the sampling interval. All serum concentrations were normalized to a common dose of 10 mg.

Statistical analysis of the PID scores, the VAS differences, and the serum concentrations for the 3 groups were carried out by means of paired Student's t-tests and paired Wilcoxon tests. The BMDP-programs were used for the regression analysis.

Results

Limitations of data. One patient (No. 5, not shown in Table 1) had to be excluded from the study as he was so fast asleep after dosing with the mixture that he was unable to cooperate. The serum concentration of ketobemidone approx. 4 h after dosing was 6.5 ng/ml, which is in the normal range. It has not been possible to explain why the patient reacted in this way. (The patient was asleep for approx. 16 h.) The serum concentrations for patient 7 and 8 have not been determined due to interfering peaks in the chromatograms (patient No. 7) and too many (more than 30%) samples with concentrations below the limit of detection (patient No. 8).

Serum concentrations of ketobemidone and A29. The serum concentration time curves of ketobemidone for each patient in the study are shown in Fig. 1. All patients, except patient No. 6, have the 3 curves close together. Patient No. 6 has the curve for the mixture well above the 2 curves obtained after dosing with the tablets. It has not been possible to find an explanation for the lapse of the curves.

The serum concentration time curves of the spasmolytic substance A29 resembled those of ketobemidone. The absolute concentrations of A29 were, however, higher in accordance with the higher doses of this compound (see note on page 583). The pharmacokinetic profile of the spasmolytic substance and ketobemidone are alike and the presence of A29 does not influence the kinetics of ketobemidone (1, 3, 5). Due to this fact, and as we consider ketobemidone the most important analgesic compound, we have only considered the ketobemidone concentrations in the comparison between the tablets and the mixture.

Serum half-life for ketobemidone. Sufficient data on the serum concentration time curves were available in 10 patients for determination of the serum half-life of ketobemidone for the first tablet, the mixture, and the second tablet. The mean serum half-life of the first tablet was 2.39 h ±0.49 (SD), the mixture 3.34 h ±0.92 (SD) and the second tablet 2.58 h ±0.99 (SD). No significant differences were present between the data, and the mean value for all half-lives was 2.74 h ±0.90 (SD).

Comparison of serum concentrations for tablet 1—mixture—and tablet 2. In order to obtain AUC values which could be compared statistically some of the curves in Fig. 1 had to be slightly modified. These modifications were typical: the last sampling times were not used in all cases or missing values at specific sampling times were in some cases calculated as a mean value of two other values.

The areas under the serum concentration time curves after these changes, together with the calculated average serum concentrations for each patient, are shown in Table 3. These concentrations were calculated from the 'true' areas as they are independent of the length of the sampling interval.

After correction to a dose of 10 mg of the values for patient No. 2 and 3 (Table 3) comparison by means of paired Student's t-tests and a paired Wilcoxon-test showed no differences for the AUC under the serum concentration time curves ($p>0.05$). Nor could any differences be demonstrated in comparing the average serum concentrations ($p>0.05$). Consequently, there are no significant differences in the measured serum concentrations for the 3 treatments (first tablet, mixture, second tablet).

Relative bioavailability. The relative bioavailability for each patient has been calculated by dividing the AUC for

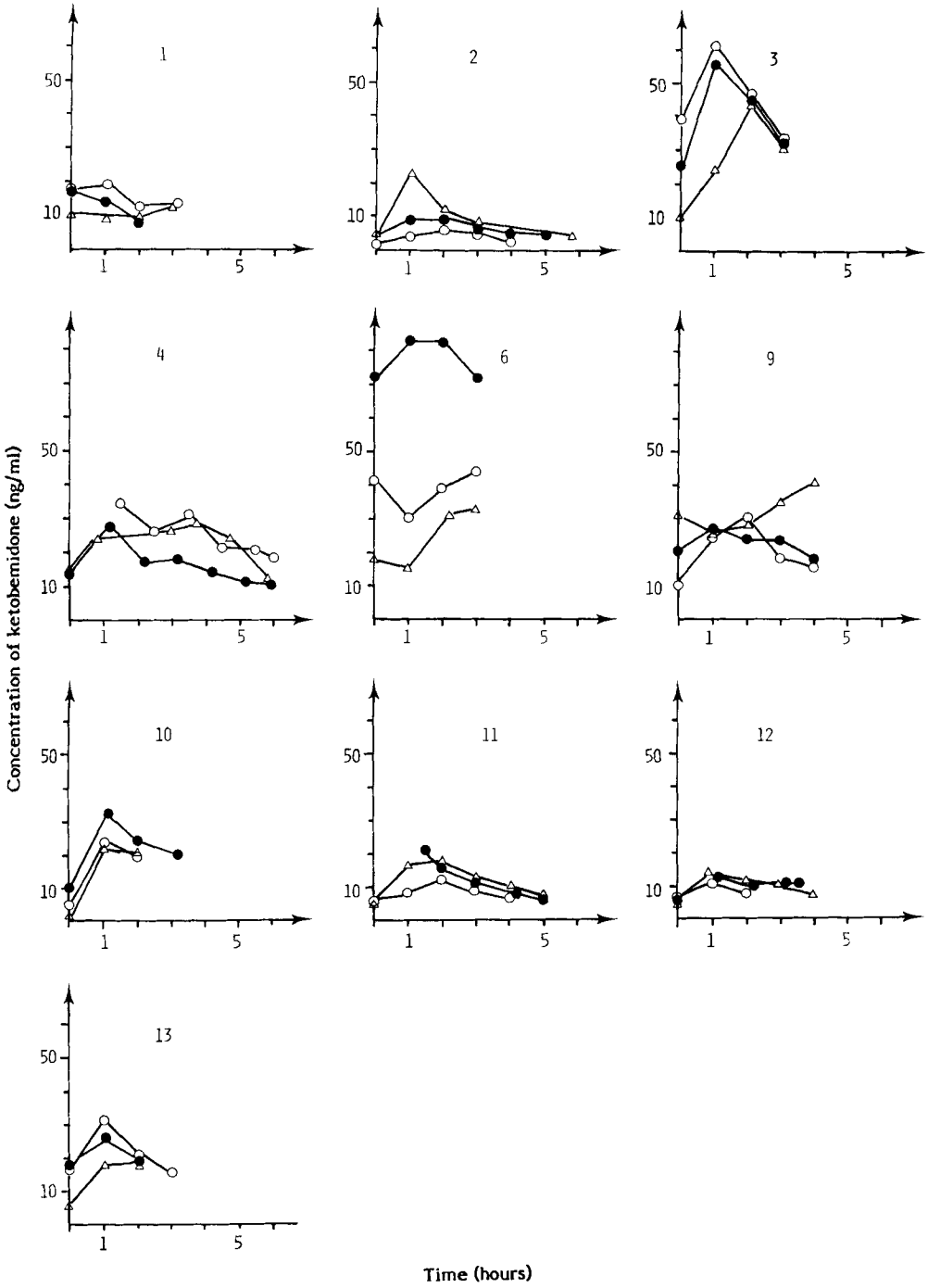

Fig. 1. Serum concentration time curves of ketobemidone for each patient. △—△, first tablet, ●—●, mixture, ○—○, second tablet.

the mixture by the mean value of the AUC for the 2 tablets. The mean value was 124±55. With the exclusion of patient No. 6 the mean value obtained was 108±24 which is close to 100%, as could be expected from the serum concentrations and the AUC for the 3 groups.

Normalization to a common dose of 10 mg ketobemidone. All measured serum concentrations have been normalized to a common dose of 10 mg ketobemidone. The calculated concentrations are shown in Fig. 2. Data on the mixture without patient No. 6 has been shown as a separate curve. Only sampling times with at least 2 individual concentrations have been included. The curves were ex-

Table 3

The areas (AUC) under the serum concentration time curves, and average serum concentrations for each patient in each blood sampling interval

Pat. No.	Dose (mg)	AUC (serum), ng·h·ml^{-1}			Average serum concentration, ng/ml		
		First tablet	Mix-ture	Second tablet	First tablet	Mix-ture	Second tablet
1	10	19.6	26.7	33.5	10	13	15
2	5	53.0	35.1	19.5	10	7	4
3	15	89.1	127.1	145.4	30	43	49
4	10	137.6	101.4	153.6	24	17	26
6	10	65.6	237.1	111.8	23	79	37
7	10	–	–	–	–	–	–
8	5	–	–	–	–	–	–
9	10	126.8	95.1	87.0	32	24	21
10	10	33.0	54.1	36.4	17	24	18
11	10	66.5	61.2	43.0	13	12	9
12	10	44.2	38.6	19.3	11	11	10
13	10	35.1	46.7	47.9	17	22	22

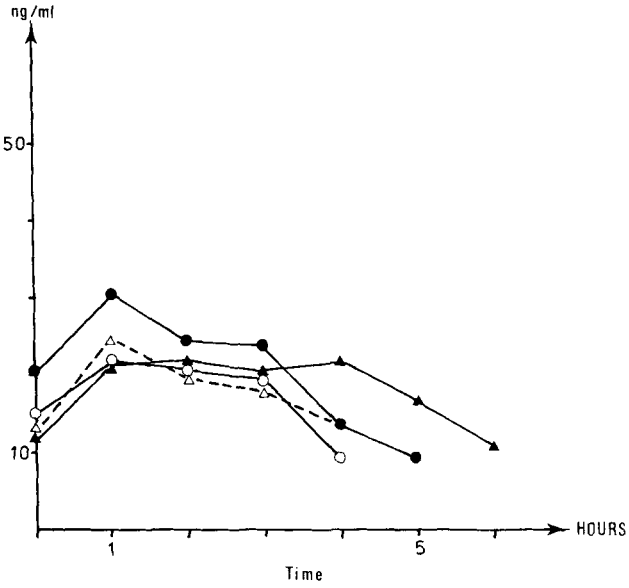

Fig. 2. Normalized serum concentrations of ketobemidone (10 mg). ▲—▲, first tablet, ●—●, mixture, ○—○, second tablet, △—△, mixture without patient No. 6.

Table 4

The areas (AUC) under the VAS difference and the PID scores for each patient

Pat. No.	Dose	AUC (VAS-differences)			AUC (PID)		
		First tablet	Mix-ture	Second tablet	First tablet	Mix-ture	Second tablet
1	10	107	82	33	3.5	2.5	0.5
2	5	45	25	2	1.5	0.5	0.5
3	15	22	16	30	0.5	0.5	3.5
4	10	143	3	13	8.0	0.0	0.0
6	10	14	143	9	1.0	4.5	1.0
7	10	24	84	21	2.5	3.2	1.0
8	5	10	5	47	1.0	0.5	1.0
9	10	17	30	10	4.0	–	–
10	10	97	50	179	4.0	2.5	6.5
11	10	68	44	16	5.0	0.5	0.5
12	10	15	12	15	2.0	0.0	4.0
13	10	69	79	67	1.0	1.5	0.5

Table 5

Side effects registered during the study

	No. of patients		
	Tablet 1	Mixture	Tablet 2
Sedation	3	1	1
Dizziness	2	1	2
Depression	1	–	1
Nausea	2	2	3
Sweats	–	3	1
Thirst (Dry mouth)	5	6	3

pected to be close to each other as no differences were detected between the 3 groups. Fig. 2 shows that this is in fact the case.

Effect parameters—analgesic effect of ketobemidone. The areas under the VAS-difference and the PID-scores are shown in Table 4. No significant differences could be demonstrated in analgesic effect, and duration of analgesic effect between the first tablet—the mixture—and the second tablet as judged by the present effect parameters ($p>0.05$).

Relations between serum concentration of ketobemidone and effect parameters. Linear regression analysis was performed on the following parameters:

— Mean dose of ketobemidone vs. AUC for serum concentration, AUC for VAS differences, AUC for PID and no correlations was found.

— When analysing each individual patient—serum concentration of ketobemidone vs. VAS—a significant correlation, ($p<0.05$) was found in 2/13 and no correlation in 11/13 patients.

— When analysing VAS vs. serum concentrations of ketobemidone for all patients for tablet 1—mixture—tablet 2 separately a significant correlation was found ($p<0.05$) for tablet 1 and the mixture but not for tablet 2.

The variations in AUC for PID were too small for analysis.

Side effects. Very few side effects were seen during the treatment period. 2/12 patients did not have any side effects at all. 10/12 patients had a variety of grade 1–2 side effects, the most common being thirst—dry mouth evidently due to the spasmolytic compound A29—followed

by sedation, nausea, and dizziness. The side effects are summarized in Table 5.

No significant differences were present between the tablets and the mixture and too few side effects were present for a more detailed analysis.

Discussion

The first aim of the present study was to compare Ketogan tablets and Ketogan mixture with regard to serum concentrations of ketobemidone, analgesic effect, duration of analgesic effect and side effects. Under the conditions chosen for the study these parameters were fairly similar after administration of tablets and mixture. A mean serum half-life of 2.74±0.90 h is consistent with data from earlier studies on the pharmacokinetics of ketobemidone (1, 2, 4, 5).

The second aim was to investigate the possible correlation between the serum concentration of ketobemidone and the analgesic effect and side effects. Too few side effects for analysis were registered during the study. No clearcut correlation between serum concentrations and analgesic effect was found when analyzing all data in the study. Only when the 3 treatments, tablet 1—mixture —and tablet 2, were analyzed separately a significant correlation was obtained between the VAS-scores and the serum concentrations after dosing with the first tablet, the mixture, but not with the second tablet.

Several explanations may exist to account for this phenomenon:

1) We have earlier shown (7) that there is a linear correlation between VAS difference scores and PID, but because of the non-categorial nature of the VAS score this is a much more sensitive parameter than the PID.

2) It must be stressed that all the patients in the study were on a fixed time dosing schedule with Ketogan. They were therefore remedicated in order to prevent pain relapse and not at recurrence of pain. This may indicate that the serum concentration time curves and the effect curves have been cut off, leaving out some data which might have been important in this respect.

3) When patients with pain are hospitalized under comfortable conditions without the anxiety in their domestic situation they will often experience a gradual decrease in their pain and demand for analgesics. When analyzing AUC for VAS difference scores for day 2, 4 and 6 in the present study a marginally significant decline was present with time. This may well explain why the correlation could be demonstrated on day 2 and 4, but not on day 6.

In conclusion, Ketogan given as tablets or mixture is an effective drug in controlling chronic pain of malignant origin for prolonged periods of time with limited side effects. Its main limitation is its relatively short half-life leading to an effective pain relief in the order of 3–4 h. An important task should be to develop a ketobemidone tablet with sustained release and a significantly longer duration of pain relief.

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REFERENCES

1. Andersson P., Arnér S., Bondesson U., Boréus L. O. and Hartvig P.: Clinical pharmacokinetics of ketobemidone. Its bioavailability after rectal administration. Eur. J. Clin. Pharmacol. 19 (1981), 217.
2. — — — — — Single-dose kinetics and bioavailability of ketobemidone. Acta Anaesth. Scand. (Suppl.) 74 (1982), 59.
3. — — — — — Pharmacokinetics of ketobemidone. Adv. Pain Res. & Ther. 8 (1986), 171.
4. Bondesson U., Arnér S., Andersson P. and Hartvig P.: Clinical pharmacokinetics and oral bioavailability of ketobemidone. Eur. J. Clin. Pharmacol. 17 (1980), 45.
5. — Tamsen A., Dahlström B. and Hartvig P.: Multiple dose kinetics of ketobemidone in surgical patients. Acta Anaesth Scand (Suppl.) 74 (1982), 63.
6. Kjaer M., Henriksen H. and Knudsen J.: A comparative study of intramuscular buprenorphine and morphine in the treatment of chronic pain of malignant origin. Br. J. Clin. Pharmacol. 13 (1982), 487.
7. — and Nielsen H.: The analgesic effect of the GABA-agonist THIP in patients with chronic pain of malignant origin. A phase 1–2 study. Br. J. Clin. Pharmacol. 16 (1983), 477.
8. Nielsen H.: Use of enzymatic solubilization of tissues and direct injection on pre-columns of large volumes for analysing biological samples by high-performance liquid chromatography. J. Chromatogr. 381 (1986), 63.
9. Twycross R. G.: Incidence of pain. *In:* Pain relief in cancer, p. 5. Edited by R. G. Twycross, Clinics in Oncology. W. B. Saunders Co., London, Philadelphia, Toronto 1984.