THE ANALGESIC EFFECT OF THE GABA-AGONIST THIP IN PATIENTS WITH CHRONIC PAIN OF MALIGNANT ORIGIN. A PHASE-1-2 STUDY.

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- 1 Fourteen patients with chronic pain of malignant origin were treated with escalating doses of THIP intramuscularly 5–30 mg in an open phase 1 study.
- 2 Analgesic activity was demonstrated in 60% of the patients at the level of 20 mg THIP and a dose response relation was present.
- 3 Side effects, sedation, dizziness, euphoria, nausea, and blurred vision were present in up to 80% of the patients and were dose limiting.
- 4 The maximum serum concentration was reached within 1 h after dosing in 87% of all administrations. Mean $t_{1/2}$ was 1.52 ± 0.63 h and the clearance was 0.49 ± 0.18 l min. Significant correlations were demonstrated between serum concentration, dose of THIP, analgesic effect and side effects.
- 5 It is concluded that THIP cannot be used for the treatment of chronic cancer pain, not because of insufficient analgesic effect but because of unacceptable side effects.

Keywords THIP chronic pain GABA-agonist analgesia

Introduction

THIP, (4,5,6,7 tetrahydroisoxazolo [5,4-c] pyridin-3-ol) is a newly synthesized structural analogue to muscimol and a specific agonist of the GABA transmitter system which has shown sedative and analgesic properties in experimental systems (Hill *et al.*, 1981, Christensen & Larsen, 1982).

Studies in healthy human volunteers have shown that doses of 10 and 20 mg intramuscularly are easily tolerated without changes in respiratory function, plasma cortisol, prolactin or glucose (Lindeburg *et al.*, 1983). Oral doses up to 120 mg day have been administered without adverse effects on vital signs (Korsgaard *et al.*, 1982).

Despite recent progress in the understanding and treatment of chronic cancer pain, most of our centrally active drugs exert their effect over the opiate receptor system (Snyder, 1978) leading to a pronounced analgesic effect, but also to the wellknown side effects of sedation, nausea, vomiting and dizziness. As THIP is active over a receptor mechanism different from that of the opiates (Christensen & Larsen, 1982; Christensen *et al.*, 1982) it was considered of interest to perform a systemic investigation of the analgesic effect and the side effects of THIP.

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Methods

Patients

Fourteen patients with moderate to severe chronic cancer pain, five men and nine women, median age 59 years, range 31–68 years, were included in the study. Data concerning sex, age, diagnoses, and localization of the pain are shown in Table 1. The median performance status was 2, range 1–3 (Zubrod *et al.*, 1960), median weight 60 kg, range 40–85 kg. Three patients had bone pain, six patients visceral pain, and five patients both types of pain with a median duration before THIP-treatment of 6 months, range 1–24 months.

All patients had histologically proven and often heavily treated malignant disease in a relatively advanced stage (Table 1).

None of the patients had previously received regular doses of opiates. The basis for the selection of patients to the study was persistent pain where aspirin, dextropropoxyphene or paracetamol were no longer effective in controlling the pain.

All patients gave informed consent to participate in the study and agreed to spend at least 1 week in hospital. Patients with marked ventilatory impairment or persistent mental confusion were not included in the study. The general and mental condition of the patients was such that they were ambulatory

Table 1 Patients' characteristics and number of dose levels studied in 14 patients with chronic cancer pain

Patient number	Sex	Age (years)	Weight (kg)	Perf. status	Diagnosis	Localization of pain	THIP (mg i.m.)					
							5	10	15	20	25	30
1	F	58	56	2	Cancer of the bladder	perivesical	+	+	+	+		
2	M	64	74	2	Cancer of the bladder	perivesical right + left hip	+	+	+	+	+	+
3	F	31	55	1	Cancer of the cervix uteri st. II B	perirectal	+	+	+	+	+	
4	M	59	70	3	Prostatic cancer st IV bone metastases	hip, knee		+	+	+		
5	M	57	60	2	Prostatic cancer bone metastases	both legs		+	+	+	+	
6	M	63	70	2	Rectal cancer	perirectal, hips		+	+	+	+	
7	F	62	53	2	Cancer of the corpus uteri bone metastases	pelvis		+	+	+	+	
8	F	66	44	3	Cancer of the colon abdominal relapse	abdomen right leg		+	+			
9	F	68	40	2	Cancer of the cervix uteri st. II B	abdomen, left leg		+	+			
10	F	60	60	2	Breast cancer, liver and bone metastases	back, pelvis		+				
11	M	59	84	1	Cancer of the right tonsil	throat		+				
12	F	54	59	2	Ovarian cancer st. IV	abdomen		+				
13	F	64	67	2	Ovarian cancer st. IV	abdomen		+	+	+		
14	F	47	85	2	Cancer of the cervix uteri st. III B	abdomen		+	+	+		
Total							3	14	11	9	5	1

and able to cooperate verbally in the assessment of their pain and general condition during the study.

Design of the investigation

Open phase 1 study in hospitalized patients with intensive observation 8 h after a single i.m. injection and daily dose escalations from 5 to 30 mg of THIP on consecutive days or until unacceptable side effects.

THIP ampoules 1 ml, 10 mg/ml, and tablets 5 mg and 10 mg were supplied by H. Lundbeck & Co, A S, Copenhagen. Patients fulfilling the criteria for inclusion in the study were admitted to the Department of Oncology. All assessment and recordings were undertaken by the same trained nurse observer for all patients in the study.

The morning after admission the first injection was given at 07.30 h. Data were recorded prior to (0), and at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h following administration. The parameters followed for each patient were of two categories:

(1) Recordings by the nurse observer.

These include pain intensity graded 1–3, 13 side effects, and the degree of side effects graded 1–3.

Moreover, pulse rate, systolic and diastolic blood pressure, and respiratory rate were recorded at each observation time. The time to remedication was noted (Kjaer *et al.*, 1982).

(2) Recordings by the patient.

Visual analogue scales (VAS), placed horizontally, length 100 mm, marked unbearable pain—no pain, were used. Recordings were made at the same observation times as those performed by the nurse observer. The patient was without knowledge of his/her prior recordings.

No analgesic or sedative was administered less than 6.5 h prior to the study medication. Drugs allowed in the test period (after the 8 h observation period or as remedication in the observation period) were the following:

Aspirin 1000 mg, paracetamol 1000 mg, diazepam 5 mg.

All other non-analgesic medications were recorded. In case of acceptable side effects the next dose in the dose escalation was given the following morning at 07.30 h and all recordings were repeated. Dose escalations were performed according to the following schedule: 5, 10, 15, 20, 25, and 30 mg. In case of

unacceptable side effects further dose escalation was stopped.

If satisfactory analgesic effect with acceptable side effects was reached, oral treatment with THIP as a single drug 10–15 mg 3–4 times daily was started and the observation was continued once a week in the out-patient clinic where pain intensity, side effects and VAS were recorded. The treatment continued until unsatisfactory analgesic effect or unacceptable side effects occurred.

Blood samples

The following blood analyses were performed in all patients before start of THIP and repeated after termination of the study:

haemoglobin, WBC, thrombocytes.
creatinine, sodium, potassium.
bilirubin, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and prothrombin time.

Blood samples (10 ml) for the determination of THIP serum concentrations were taken in 13/14 patients at each observation time for all doses tested. Serum was separated by centrifugation and kept frozen (-18°C) until analysis.

Drug analysis

The serum concentrations of THIP were determined by h.p.l.c. after cation exchange and derivatization with dansyl chloride (Madsen, 1983).

Data treatment

After termination of the study the following parameters were calculated: Pain intensity difference scores (PID) for each patient at all dose levels tested at each observation time were calculated by subtracting the pain intensity score at each observation time from the pain intensity score prior to drug administration.

VAS difference scores for each patient at all dose levels tested at each observation time were calculated in the same way as PID.

Mean PIDs and VAS difference scores for each dose level were plotted against time. In calculating the mean values for those patients who were re-medicated during the 8 h observation periods, a PID or VAS difference score of zero were assumed at all observation times after they were re-medicated.

The areas under the curves (AUC) were calculated as described for the THIP serum concentrations and comparisons performed as described in the statistical analysis.

The severity of each side effect for each patient was rated using a 0–3 scale and the ratings were summarized for each patient at each sampling hour giving the sum of side effects.

Serum concentrations

The elimination constant (β) and the half-life were calculated using the terminal part of the serum concentration-time curve ($t_{1/2} = \ln 2/\beta$). The areas under the curves were calculated by the trapezoidal rule in the time interval $0-t'$ where t' is the time of the last blood sample. The remaining area was calculated by dividing the serum concentration at t' with β . Clearance was calculated by dividing the dose by the total area and the patient's body weight.

Statistical analysis

The statistical analysis of the data was carried out by means of regression analysis, analysis of variance, and the F-test (Glim, release 3, Baker & Nelder, 1978). The analysis was performed for each patient and the material as a whole. The PID parameter and the sum of side effects were considered to be discrete variables.

Results

Efficacy

In Table 2 is shown the number of patients with analgesic effect of THIP at the different dose levels, the time from injection to the analgesic effect, and the duration of the analgesic effect. The data are based exclusively on the VAS. The effect on a VAS is defined as a decrease of 10 mm or more from the baseline (time = 0) score. The time to effect is measured in h from the injection until the earliest observation time where a decrease as defined is registered. The duration of effect is measured in h and defined as the time interval in which the above mentioned decrease can be registered.

In Figures 1 and 2 are shown the mean PIDs and mean VAS differences vs time at each dose level.

Side effects

In Table 3 are shown the five side effects which were registered in more than two patients. Side effects found only in an occasional patient were: cramp in the legs, paresthesia in hands and feet, and a 'closed' sensation in the head.

The most common side effects were sedation and dizziness occurring in 33–80% and 36–78% of the patients, respectively, with a tendency to be more frequent at the higher dose levels. In two patients sedation was so pronounced that they were fast asleep for 4–5 h. Nausea and vomiting was not a significant problem. A definite sensation of euphoria was present in some patients. They did not find it unpleasant, but felt as if they had been drinking 'a couple of beers too much'. A special side effect was the occurrence of

Table 2 Summary of efficacy analysis based on VAS data

Dose THIP (mg)	Number of patients	Number of patients with effect	Time to effect	Duration of effect
5	3	0	—	—
10	13	5	1 h (0.25–1.5 h)	4.75 h
15	9	5	0.5 h (0.25–0.75 h)	3.0–7.5 h
20	8	5	0.5 h (0.25–1.5 h)	4.5 h (2.75–7.5h)
25	4	2	0.75–3 h	5–7.25 h
30	1	1	0.5 h	7.5 h

blurred vision. The patients were unable to read or watch television, and some of the patients had to lie down with their eyes closed for 30 min–1 h after injection. The side effects began 30–45 min after injection and lasted 1–2 h.

Time to remedication

Remedication is defined as return of persistence of pain to such a degree that the patient asks for remedication before the end of the 8 h observation period.

Seven patients were remedicated at one or more occasions. Two patients were remedicated at all dose levels tested. The median time to remedication was 3.5 h (range 1–6 h) with no difference between the lower and the higher dose levels.

Vital signs

No significant change in systolic, diastolic blood pressure, pulse rate or respiratory rate were observed in any of the patients at any of the dose levels tested.

Figure 1 Mean pain intensity difference (PID) at each observation time after intramuscular injection of THIP 5–25 mg.

Figure 2 Mean visual analogue scale (VAS) difference at each observation time after intramuscular injection of THIP 5–25 mg.

Blood analysis

No significant changes in the blood analyses performed before and after THIP-treatment could be detected.

THIP serum concentrations

Table 4 gives a summary of the pharmacokinetic parameters. THIP showed linear kinetics as the AUC and the maximum concentration were proportional to the

Table 3 Summary of side effects (%)

	Dose THIP (mg)					
	5	10	15	20	25	30
Sedation	–	6 (43)	5 (45)	3 (33)	4 (80)	1
Dizziness	1	5 (36)	7 (64)	7 (78)	3 (60)	–
Euphoria	1	–	1	2	2	1
Nausea	–	3	1	2	–	–
Blurred vision	–	2	2	–	1	–
Number of patients	3	14	11	9	5	1

Table 4 Summary of pharmacokinetic parameters

Patient	$t_{1/2}$ (h)	β (h ⁻¹)	AUC Dose (h l ⁻¹)	Clearance (l h ⁻¹ kg ⁻¹)
1	1.50 ± 0.27	0.47 ± 0.08	0.043 ± 0.007	0.43 ± 0.07
2	1.32 ± 0.60	0.61 ± 0.24	0.031 ± 0.002	0.43 ± 0.03
3	1.15 ± 0.33	0.65 ± 0.20	0.029 ± 0.002	0.63 ± 0.05
4	0.55 ± 0.10	1.29 ± 0.24	0.038 ± 0.019	0.45 ± 0.20
5	1.11 ± 0.09	0.63 ± 0.05	0.031 ± 0.005	0.55 ± 0.08
6	1.46 ± 0.45	0.50 ± 0.18	0.041 ± 0.007	0.35 ± 0.06
7	0.95 ± 0.29	0.80 ± 0.29	0.025 ± 0.007	0.79 ± 0.20
8	1.50 ± 0.28	0.47 ± 0.09	0.049 ± 0.008	0.47 ± 0.08
9	1.71 ± 0.39	0.42 ± 0.10	0.048 ± 0.0002	0.52 ± 0.00
10*	2.27	0.31	0.038	0.44
11*	1.23	0.57	0.019	0.63
12*	2.99	0.23	0.096	0.18
13	2.01 ± 0.36	0.35 ± 0.06	0.040 ± 0.006	0.38 ± 0.06
Mean	1.52 ± 0.63	0.56 ± 0.27	0.041 ± 0.019	0.48 ± 0.15

* Only one dose

Figure 3 THIP serum concentration-time curve normalized to THIP dose of 10 mg. The points are given as mean ± s.d. The numbers in brackets are the number of serum concentrations used for construction of the curve at each sampling time.

Table 5 Results from the analysis of variance for the material as a whole according to the model $y = \mu + Pt + t + x$

y^x	Dose	Serum concentration	PID	VAS differences	Sum of side effects
Serum concentration	$P < 0.001$ $r = 0.81$		$P = 0.18$ $r = 0.07$	$P < 0.001$ $r = 0.26$	$P < 0.001$ $r = 0.76$
VAS differences	$P < 0.001$ $r = 0.47$	$P < 0.001$ $r = 0.46$	$P < 0.001$ $r = 0.65$		$P < 0.001$ $r = 0.49$

dose. The serum concentration–time curves for each patient showed that the maximum concentration was reached within 1 h after dosing in 87% of all THIP administrations, while the remaining 13% showed maximum after 1.5 or 2 h. A secondary peak appeared in most patients; however, the peak did not appear at the same sampling hour in all patients. All serum concentrations were normalized to doses of 10 mg and a mean serum concentration time curve was constructed (Figure 3).

Reasons for patients going off study

Three patients had to stop THIP because of lack of effect, and three patients because of unacceptable side effects. Three patients stopped treatment for other reasons, one because of start of radiotherapy, one because of lack of compliance, and one because she developed ileus and had an operation performed.

Statistical analysis

The variation between patients was rather large and as a consequence individual contributions from each patient (pt) had to be considered in the analysis of variance. As the parameters are a function of the sampling time a time contribution (t) was considered too. The general model was $y = \mu + pt + t + x$ where μ is the grand mean and (y, x) is one of the combinations (serum concentration, sum of side effects), (VAS differences, dose), (VAS differences, serum concentration), or (VAS differences, sum of side effects). Serum concentration–PID, serum concentration–VAS differences, and VAS differences–PID were compared directly while serum concentrations were compared to the dose at each sampling time. The result of the statistical analysis is shown in Table 5 where only y and x are shown.

All correlations except the correlation between serum concentration and PID were highly significant. A correlation exists between serum concentration and VAS differences although the large variation in the material results in a correlation coefficient of only 0.26. VAS differences were also significantly correlated to dose, but again with a low correlation coefficient. The sum of side effects correlated significantly to serum concentration with a relatively high correlation coefficient ($r = 0.76$).

From the data it can be deduced that concentrations higher than $0.55 \mu\text{M}$ THIP resulted in side effects. Furthermore it was shown that the difference in serum concentration from one level of sum of side effects to the next was small.

The correlation between the two effect parameters was rather good and the data showed that one PI step equals 22 mm (average, range 18–26 mm) on the VAS, and $PI = 0$ was -0.84 ± 1.1 (s.e. mean) mm on the VAS.

The maximum of the sum of side effects was 6, and the correlation between VAS differences and sum of side effects showed that patients having a sum of 4, 5, or 6 had a VAS difference which was 12 mm (average, range 10–14 mm) lower than the rest. Sums of side effects of 0, 1, 2, or 3 had no effect on the VAS.

The interpatient variation was very large and resulted in low correlation coefficients for the material as a whole (Table 5), so it was decided to run the analysis of variance for each patient. Because of the limited number of observations of side effects in each patient it was not possible to include this parameter in the analysis. Also the PID had to be excluded from the analysis because many of the recordings were zero. Furthermore patients 8, 9, 10, 11 and 12 had not enough degrees of freedom to be included in the analysis.

The analysis of variance for each patient (numbers 1, 2, 3, 4, 5, 6, 7 and 13) showed that all correlations of serum concentration to the dose were significant ($P < 0.005$) with correlation coefficients between 0.89 and 0.98. Only patients 1 and 2 had a significant correlation between VAS differences and serum concentration ($P < 0.02$). The correlation coefficients were 0.94 and 0.80, respectively.

Figure 4 shows the mean area under the PID and VAS differences in the 8 h observation period as a function of dose. It is observed that the curves bend for the higher doses of THIP.

Discussion

The results from the present study show that THIP has analgesic effect when administered to patients with chronic cancer pain. The effect starts rapidly after administration, 30–45 min, and lasts 3–7 h. The analgesic effect is correlated with the serum concentra-

Figure 4 Mean areas under the PID (●) and VAS (○) difference curves (AUC) in the 8 h observation period as a function of THIP dose.

tion of THIP. These observations support the findings in animal models (Christensen *et al.*, 1982; Hill *et al.*, 1981; Christensen & Larsen, 1982). The main problem is the dose-limiting side effects of which sedation and dizziness are the most predominant. The development of side effects is closely correlated to the serum concentration of THIP as it could be shown that concentrations above $0.55 \mu\text{M}$ resulted in side effects. The side effects became especially predominant when THIP was administered as tablets in repeated doses over the day. Although the analgesic effect was satisfactory, most patients found that they were unable to function normally because of sedation, dizziness and blurred vision.

The clinical observations from the present study support that THIP does not exert its effect over the opiate receptor system as there was no effect on pulse rate, blood pressure and respiratory rate. Moreover, the side effects were quite different from those seen during treatment with opiates, and there was no tendency towards diminishing side effects with time.

The half-life of THIP, 1.52 h, is in good agreement with the value found earlier in human volunteers

(Schultz *et al.*, 1981). As seen from the short half-life and the high clearance THIP is quickly eliminated mainly by excretion as unchanged THIP in the urine (Schultz *et al.*, 1981). The appearance of secondary peaks on the serum concentration-time curves are hard to explain, one explanation, however, could be an enterohepatic circulation of THIP or a metabolite (glucuronic acid conjugate which could break down to THIP).

The reason why serum concentration is correlated to one of the effect parameters and not to the other is most likely that the VAS scale consists of 100 steps while the PI scale only has 4. On assumption that the PI steps are equal the theoretical value for one PI step on the VAS scale is 25 mm. The value found here (22 mm) can justify the use of only one of these scales for evaluation of pain as they give the same amount of information. The influence of the sum of side effects on the VAS indicates that the patients cannot separate the analgesic effect from the side effects, but tend to evaluate their overall situation. Sums of side effects of 4, 5, or 6 occurred mainly at doses of 20 and 25 mg of THIP where the predominant side effects were sedation and dizziness. As a consequence THIP will be evaluated more pessimistically by patients with these side effects compared to patients without, and the area under the VAS-time curve for higher doses of THIP will be lower than expected. Therefore one would expect a deviation from a straight line for the VAS areas for doses higher than 15 mg. In fact a decrease is observed for 25 mg. Surprisingly, the same effect is observed for the PID areas where a decrease is observed for doses higher than 15 mg (Figure 4). This means that the nurse observer also to some extent evaluates the patient's overall condition and not only the analgesic effect. However, the investigation was not designed to illustrate this phenomenon, which must be the subject of a separate study.

A phase 2 study with oral THIP 15 mg 3–4 times daily in eight patients showed a median duration of treatment of 14 days, range 2–120 days. 71% of the patients went off study because of unacceptable side effects, essentially the same as those found in the phase 1 study.

Seen from a practical point of view in treating cancer patients with chronic pain THIP cannot be used in its present form. It is possible that the development of a sustained release formulation could avoid the serum concentration peak and thus result in a formulation which might be administered with fewer side effects.

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