EFFICACY OF PHENYTOIN SODIUM IN THE MANAGEMENT OF POST OPERATIVE PAIN

G. A. ESSIET,* A. ESSIET AND J. O. AKPAN***

Departments of Pharmacology and Surgery**, College of Medical Sciences*
University of Calabar, Calabar, Nigeria.

Summary: Postoperative pain in three groups of Nigerian patients, comprising 15 cases each of minor, intermediate and major surgical operations, was treated with phenytoin sodium, dihydrocodeine and paracetamol respectively. The aim of the study was to determine the efficacy of phenytoin sodium as a postoperative analgesic agent. Analgesia was assessed using the results of verbal rating scale scores namely, PID (pain intensity difference), SPID (sum of pain intensity difference) and TOTPAR (total pain relief) and a modified global rating scale. The results showed phenytoin sodium to be superior to paracetamol in the treatment of all grades of postoperative pain. It was equipotent to dihydrocodeine in mild and moderate pain, while dihydrocodeine was superior in severe pain. It is concluded that Phenytoin sodium is an efficacious analgesic agent in mild to moderate postoperative pain.

***Key Woras**: Pain; Analgesia; Postoperative.*

Introduction

Medical care often involves surgical operations. A constant accompaniment of such operations is pain, which may be mild, moderate or severe, often equating in this sense, to minor, intermediate or major surgery. Conventional drugs used in the treatment of such pain are either opiates, with their well known propensity for addiction, sometimes even with a single dose (Bond, 1981) or non steroidal anti-inflammatory agents [NSAIDS], which have a propensity for causing gastric erosion (Insel, 1990). This tendency would naturally be higher in the postoperative period because of the stress of surgery and the usually starved ('empty stomach') preoperative state of some surgical patients. The desirability of having an efficacious analgesic agent devoid of the above side effects caused us to investigate a drug which though having analgesic properties and devoid of these undesirable effects, is not listed as an analgesic in the index of ethical preparations. This drug is phenytoin sodium. It is an established anti-convulsant drug (Smith *et al*, 1988) with analgesic properties (Swerdlow, 1984; Ludwig and Otto, 1982). It is not addictive as epileptics take it for prolonged periods. It is a bioelectrical modulator (Hartman *et al*, 1986) and is known to aid wound healing (Smith *et al*, 1988).

Approval for the study was obtained from the ethical committee of the University of Calabar teaching hospital where most of the study was conducted and all patients recruited into the study, gave informed consent.

Patients and methods.

Using an open non-crossover method, the analgesic efficacy of phenytoin sodium in the treatment of postoperative pain was assessed against those of representatives of two groups of standard analgesic agents, namely dihydrocodeine and paracetamol. The surgical operations were categorized as minor, intermediate and major. Included in the 'minor' group were operations involving minimal tissue damage like excision of subcutaneous lipomata and other small lumps. The 'intermediate' group comprised operations involving more extensive dissections than the minor group e.g. uncomplicated herniorrhaphies, varicocelectomies and hydrocelectomies. For the 'major' group were patients undergoing prostatectomy, a procedure that is a lot more invasive and involves more tissue damage than the minor and intermediate groups. Patients who had general anaesthesia for their procedures were excluded from the study, as their immediate post operative state would not be conducive for administration of the analgesic agents which were given orally nor would it allow effective verbal communication. All the patients recruited into the study were made to score their baseline pain intensity (which is the first experience of pain post operatively), using the verbal rating scale (Sunshine *et al*, 1993) as 0 for no pain; 1 for mild pain; 2 for moderate and 3 for severe pain. The appropriate drugs were then administered and the scoring repeated in the first half hour and then hourly for eight hours. All drugs were administered orally giving the highest tolerable and safe dose of each drug as follows: phenytoin sodium (epanutin, Parke-Davis) 100 mg three times /day; paracetamol (panadol, Smith Kline Beecham) 1g three times/day and dihydrocodeine tatrate (DF.118, Glaxomed) 80 mg three times/day. Administration of the medications was continued and at the end of 48 hours the patients were caused to grade their overall pain management, using a modified global rating

scale as 1 for Poor; 2 for Fair and 3 for Good. (modified from Sunshine *et al* 1993). Patients not having significant pain relief after two doses were given the more potent analgesic, intramuscular pethidine 100mg 4-6hourly as appropriate and excluded from the study

Measurements of analgesia (after Laska et al., 1967) Pain intensity difference [PID] scores were calculated for each observation and the sum of pain intensity difference [SPID] obtained by adding hourly PID scores. Total pain relief scores [TOTPAR] were obtained from the sum of hourly pain relief values weighted by the time interval between observations. Peak percentage PID, the 'maximum achieved pain relief score' divided by the 'maximum attainable pain relief score' multiplied by 100 was worked out for each group. Data obtained were subjected to computer analysis to determine means, percentages, standard errors and tests of significance by student-t test. Results are presented in tabular and computer generated graphic forms.

Results.

One hundred and thirty five patients were studied, 89 males and 46 females [M: F - 1.9:1]. Table1 shows the age range, weight distribution and other socio-demographic data of the patients. All patients complained of some degree of baseline pain post operatively. In the minor surgery group (n-45), 31 patients (69%) complained of mild pain, 9 (20%) of moderate and 5 patients (11%), of severe pain. In the intermediate surgery group (n-45), 7 patients (16%), had mild pain, 28 (62%) moderate and 10 (22%) severe baseline postoperative pain. In the major surgery category, 5 (11%), 12 (27%) and 28 (62%) patients complained of mild, moderate and severe pain respectively.

The results for the various modalities of pain assessment are shown in the different rows of Table2. Table 2 (i) shows the sum of pain intensity difference (SPID) as per drug treatment group. For the mild pain group, the scores were; phenytoin; 8.55, dihydrocodeine; 8.60 and paracetamol; 7.55. In the moderate pain group, phenytoin was 8.97, dihydrocodeine; 9.01 and paracetamol; 8.37. The difference was most marked in the severe pain group, with phenytoin; 10.26, dihydrocodeine; 12.39 and paracetamol; 10.10. Total pain relief scores [TOTPAR] results are shown in Table 2(ii). Scores for the mild pain group were 16.28, 16.32 and 15.70 for phenytoin, dihydrocodeine and paracetamol respectively. For moderate pain, the scores in the same order were 13.91, 13.90 and 12.29, while in the severe pain group, dihydrocodeine scored 13.00, paracetamol 10.31, and phenytoin 10.68. Patients' assessment of pain management is reflected in Table 2(iii) as the average of the Global rating scores by all the patients in each group. The scores for dihydrocodeine in mild pain (2.97) and severe pain (2.78) were higher than for phenytoin (2.93 for mild; 2.06 for severe) and paracetamol (2.50 for mild; 1.85 for severe). The score for dihydrocodeine was 2.85 and phenytoin 2.82. The global rating scores (maximum 3) and the number of patients per score, for the various pain groups following administration of the drugs is compared in Table 3. Analysis of pain relief in the different grades of postoperative pain showed that 33 patients (74%) in the phenytoin group had 'good' relief from their baseline postoperative pain. Five (11%) had 'fair' relief while 7 (15%) had 'poor' brelief.

Fig. 1 Time-effect curve for mean pain relief scores of severe pain in different study drugs

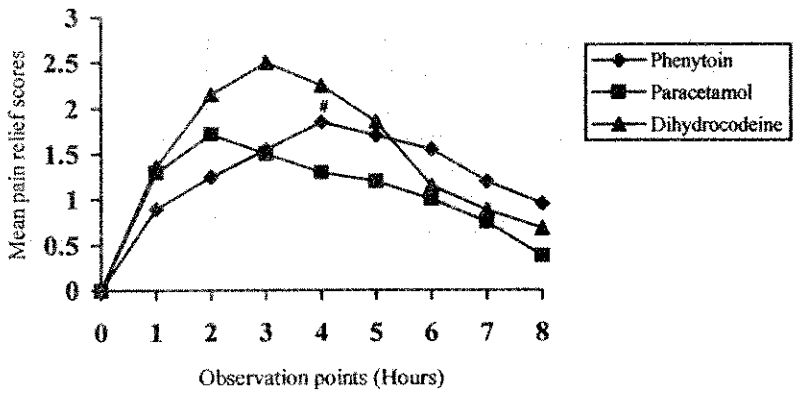

Table 1 Socio-demographic variables of patients

S/N	PATIENTS' VARIABLES	CHARACTERISTICS OF VARIABLES	NUMBER OF PATIENTS n=135	PERCENTAGES (%)
1.	Age (years)	18 – 25		
		26 – 33	9	6
		34 – 41	28	21
		42 – 49	28	21
		50 – 57	21	16
		58 – 65	27	20
		66 – 73	20	15
			2	1
2	Weight (kg)	45 - 49	6	4
		50 - 54	8	6
		55 - 59	16	12
		60 - 64	21	16
		65 - 69	28	21
		70 - 74	30	22
		75 - 79	13	10
		80 - 84	11	8
		85 - 89	2	1
3.	Sex	Males	89	66
		Females	46	34
4.	Religion	Christianity	108	80
		Islam	7	5
		Others	20	15
5.	Ethnic Background	Efik	62	45
		Northern Cross	28	21
		Riverians	28	21
		Igbo speaking	7	5
		Yoruba	5	4
		Hausa	5	4
		Others		
6.	Educational Background	No formal Education	-	-
		Primary education	26	19
		Secondary education	74	55
		Tertiary education	35	26
7.	Means of livelihood	Senior Civil Servant	26	19
		Junior Civil Servants	29	21
		Large Scale business	20	15
		Small scale business	28	21
		Farming	22	16
		Fishing	5	4
		Students	5	4

Table 2. Analgesic parameters of Phenytoin against those of Dihydrocodeine and Paracetamol

Parameters	Phenytoin group	Dihydrocodeine group	Paracetamol group
(i) SPID scores			
Mild pain	$8.55^{xy} \pm 0.02$	8.60 ± 0.02	7.55 ± 0.5
Moderate pain	$8.97^{xy} \pm 0.02$	9.01 ± 0.02	8.37 ± 0.02
Severe pain	$10.26^{xy} \pm 0.01$	12.39 ± 0.01	10.10 ± 0.01
(ii) TOTPAR scores			
Mild pain	$16.28^{xy} \pm 0.01$	16.32 ± 0.02	15.70 ± 0.03
Moderate pain	$13.91^{xy} \pm 0.01$	13.90 ± 0.01	12.29 ± 0.02
Severe pain	$10.68^{z} \pm 0.02$	13.00 ± 0.01	10.31 ± 0.02
(iii) Global Rating scores			
Mild pain	$2.93^{xy} \pm 0.04$	2.97 ± 0.03	2.50 ± 0.06
Moderate pain	$2.82^{xy} \pm 0.06$	2.85 ± 0.04	2.21 ± 0.05
Severe pain	$2.06^{z} \pm 0.07$	2.78 ± 0.06	1.85 ± 0.05
(iv) Time of PID (Hours)			
Mild pain	4.07 ± 0.13	3.03 ± 0.03	2.00 ± 0.04
Moderate pain	4.13 ± 0.13	3.03 ± 0.04	2.03 ± 0.01
Severe pain	4.20 ± 0.10	3.11 ± 0.05	2.03 ± 0.02
(v) Peak PID percentage			
Mild pain	96.5 ± 0.11	97.3 ± 0.09	84.5 ± 0.12
Moderate pain	88.5 ± 0.15	89.4 ± 0.17	73.1 ± 0.21
Severe pain	56.0 ± 0.02	81.8 ± 0.25	45.0 ± 0.25

Above results show mean ± SEM; n = 15

Key:

SPID = Sum of pain intensity difference TOTPAR = Total pain relief
PID = Pain intensity difference X = statistically, no significant difference between it and dihydrocodeine at $P < 0.05$. y = statistically, there is a difference between it and paracetamol in favor of pheytoin at $P < 0.05$. z = statistically, there is a difference between it and dihydrocodeine in favour of dihydrocodeine, at $P < 0.05$.

Table 3. *Rating of pain relief by patients following administration of the various drugs in the different pain groups*

Study Groups	Poor (1)	Fair (2)	Good (3)
Phenytoin			
Mild pain (n=15)	-	1(7%)	14(93%)
Moderate pain (n=15)	1(7%)	2(13%)	12(80%)
Severe pain (n=15)	6(40%)	2(13%)	7(47%)
Dihydrocodeine			
Mild pain(n=15)	-	1(7%)	14(93%)
Moderate pain(n=15)	-	2(13%)	13(87%)
Severe pain(n=!5)	1(7%)	1(7%)	13(86%)
Paracetamol			
Mild pain(n=15)	2(13%)	2(13%)	11(74%)
Moderate(n=15)	4(27%)	3(20%)	8(53%)
Severe pain(n=15)	7(46%)	3(20%)	5(34%)

* Significantly different from phenytoin ($p<0.05$) # Significantly different from paracetamol ($p<0.05$)

Discussion

Phenytoin sodium a drug well known for its anti-epileptic properties (Morselli and Franco-Morselli, 1980), is actually a bioelectrical modulator (Hartman *et al* 1984), a regulator of neurotransmitter effects and also a regulator of trans-membrane ionic fluxes/intracellular ionic distribution (Twombly and Narahashi, 1986). It is listed solely as an anti-epileptic and anti-arrhythmic drug (BNF, 2002), thus diminishing its other feasible clinical uses, which includes the relief of pain (Swerdlow, 1984). The efficacy of phenytoin as an analgesic has been reported only for chronic pain (Clifford and Trotter, 1984). Except for the report of treatment of the pain of acute trigeminal neuralgia (Von Albert, 1978), which is really an acute on chronic condition, the authors did not find any report in the literature on the efficacy of phenytoin in acute pain. The findings in this study clearly show phenytoin sodium as an effective postoperative analgesic agent for mild to moderate postoperative pain thus proving its efficacy in the treatment of acute pain. TOTPAR scores for phenytoin were notably higher than for paracetamol in all grades of pain (Table 2ii). Hourly pain relief scores among the different treatment groups for each class of pain showed a definite pattern. Fig.1 illustrates the pattern for severe pain. In the first four hours of observation, dihydrocodeine was leading the other drugs as follows: dihydrocodeine > paracetamol > phenytoin. During the last four hours, the scores for phenytoin increased significantly ($p<0.05$) over dihydrocodeine, such that while the effects of the other medications were wearing off, that of phenytoin reached its peak and was sustained up to about the sixth hour before decreasing. Even during the 'decreasing' phase, the scores were still relatively higher than those of dihydrocodeine and paracetamol.

Overall, the results from this study show phenytoin as being a more efficacious agent than paracetamol and comparable to dihydrocodeine in the treatment of mild to moderate postoperative pain. This property together with other known qualities of the drug, like being anti-depressant, non addictive and especially its effect on wound healing commends it as a desirable alternative to the more commonly used analgesic agents in post operative pain management.

Acknowledgements.

We thank the consultants of the department of Surgery, University of Calabar Teaching Hospital, and Gracian Clinic, Calabar who allowed the use of patients under their care for this study. This work was funded by a grant from Gracian Clinic, Calabar.

References

British National Formulary (2002). Vol. 43 pp 233.

Bond, M. R. (1981). Personality and Pain. In: Persistent pain, modern methods of treatment. Edited by Liptons, S. A. Academic Press London. Vol.2, pp1-25.

Clifford, D. B. and Trotter, J. L. (1984). Pain in multiple sclerosis. *Arch. Neurol.* 41: 1270-2.

Hartman, G. S., Flamengo, S. A. and Riker, W. F. (1986). Succinyl choline: Mechanism of fasciculations and their prevention by d-tubocurarine or diphenyl hydantoin. *Anesthesiology* 65(4), 405-13.

Insel P. A. (1990). Analgesic-antipyretics and anti-inflammatory agents; drugs employed in the treatment of Rheumatoid arthritis and agaout. In: The pharmacological Basis of Therapeutics, Eds,Gilman, A. G., Rall, T. W. Nies, A. S., and Taylor, P. Pergamon Press New York. 8th Ed. Vol. 1 pp 638-681.

Laska, E., Gormley, M., Sunshine, A. (1967). A bioassay computer programme for analgesic clinical trials. *Clin. Pharmacol. Ther.* **8**: 658-69.

Morselli P. L. and Franco-Morselli, R. (1980). Clinical pharmacokinetics of antiepileptic drugs in adults. *Pharm. Ther.* **10**: 65-101.

Smith, B. H., Bogoch, S.and Dreyfus, J. (1988). The broad range of clinical use of phenytoin. Dreyfus medical foundation. New York.

Sunshine, A., Olson, N. Z., Zighelboim, I. And DeCastro, A. (1993). Ketoprofen, acetaminofen plus oxycodone and acetaminophen in the relief of postoperative pain. *Clin. Pharm. and Therapeutics*. 54(5): 544-55.

Twombly, D. A., Narahashi, T. (1986). Phenytoin block of low threshold calcium channels is voltage and frequency dependent. *Soc. Neurosc.Abstr.* (Pt2) 1193.

Von Albert, H. H. (1978). Treatment of acute trigeminal neuralgia with intravenous infusions of phenytoin. *Much Med. Wsch.* 120(5): 529-30.

***Received**: September 16, 2003*
***Accepted**: November 6, 2003*