CLINICAL EVALUATION OF NIALAMIDE IN OBSTETRICS AND GYNAECOLOGY

A PRELIMINARY COMMUNICATION

by

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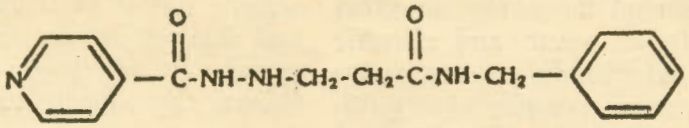
It is pain that most often brings the patient to the doctor. Relief of pain therefore wherever it be in the body, or whatever its cause, is one of the chief aims of treatment. To us obstetricians, relief of pain during labour, with no harm to mother and child and no prolongation or alteration of labour, is still a challenge. We are still in quest of some simple method or means which involves no skilled technique, no extra staff and a negligible cost.

Hence when I learnt that a few tablets of Niamid (Nialamide) given orally a couple of weeks before the date of labour reduces considerably pain during labour, relieves intrinsic dysmenorrhoea, pre-menstrual tension, post-natal depression, and menopausal psychological disturbances, I was most anxious to try the drug.

Pharmacology

Nialamide is a monoamine oxidase inhibitor. It is 1-2-(benzyl-carbamyl) ethyl-2-isonicotinoyl hydrazine (Structural Formula).



Zeller, in 1952, had shown the inhibitory effect of iproniazid (isonicotinoyl isopropyl hydrazine) on monoamine-oxidase. Meanwhile Pletscher reported elevation of brain amine contents following administration by monoamine oxidase inhibitors, bringing into focus the possible connection between enzyme inhibition and behaviour. Experiments on dogs have shown that with brain, mono-amine oxidase inhibitor Nialamide, has about twice the potency of iproniazid.

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Mode of Action

Monoamine oxidase inhibition in the central nervous system may be expected to produce elevation of brain amines, such as norepinephrine and serotonin. Hence monoamine oxidase inhibitors may be classified as central nervous system stimulant. There is evidence in literature indicating a possible relationship between brain amine content and reactivity to pain. Increase of brain amines like 5-hydroxy-tryptophane a precursor of serotinin, reduces substantially the sensitivity to pain. Substantial increase in brain amine content facilitated by Nialamide might be responsible for an alteration in perception of painful stimuli. Unlike B.-phenyl-isopropyl hydrazine and iproniazid, nialamide completely lacks hypotensive activity. There is no direct relationship between cardiovascular responsiveness and degree of monoamine oxidase inhibition.

Prof. W. Walcher of the Psychoneurological Clinc, University of Graz, Austria, reported the analgesic effect of Nialamide on acute and chronic pain associated with diseases or irritation of the central, peripheral or autonomic nervous system. He observed that nialamide has a true analgesic action probably at the level of the autonomic nervous system. This view is also supported by Thaler's report on the favourable action of nialamide in functional coronary disorders. Hence the action of the drug varies greatly depending on the vegetative constitution and the initial vegetative status of the patient. Disorders of autonomic pain path-ways appear to respond well to Nialamide. Irritation of the peripheral nervous system apparently responds better than organic disease of the central nervous system. O. Quesnel, a Neurosurgeon of Mexico, believes that because Nialamide produces psychic stimulation, it has been shown to potentiate the analgesic effect of morphia and meperedine.

Nialamide and Nitrogen Mustard have been used in the management of advanced cancer. In conjunction with nitrogen mustard gas and telecobalt therapy, Nialamide helps to improve the patient's adaptability to his disease. Though it has no analgesic action *per se* it favourably modifies the degree of pain apprehension.

Dr. Thaler of Australia seems to think that Nialamide has a characteristic ganglionic blocking agent. Monoamine oxidase has some action on the periphery, a metabolic type of effect that would alter the pain perception.

Dr. Florez Tascon of Madrid, showed by electroencephalographic studies that nialamide had a peripheral action, but it also has a very clear and distinct action on the recticular system in the brain which can be shown by electroencephalographic tracings.

The mechanism of action of this drug is still uncertain as it shows both peripheral and central points of attack. Many unknown pharmacodynamic properties of Nialamide could play an important role in the explanation of impirical clinical findings.

Toxicity

60 mg./kg./day orally for 28 days in cats and 6 months in dogs showed no damage to the liver and kidneys

at all. While 50 mg./kg. of iproniazid for five days orally, produced extensive lobular necrosis. Complete inhibition of monoamine oxidase was found in all tissues at 10 mg./kg. and higher. Most of the drug in human beings is recovered from the urine unchanged together with several unidentified urinary metabolites.

Bloom and co-workers in a metabolic study with radioactive Nialamide concluded that the Nialamide molecule is probably split at the carbamide group producing metabolites which are not related to hydrazine systems known to be toxic. This also shows that Nialamide is rapidly excreted from the body. Most of it administered orally had disppeared from plasma in 8 hours while the pharmacological effects of a single injection of Nialamide are reported to have lasted many days. Nialamide produces no change in the endocrine and metabolic functions of healthy subjects. At present the use of monoamine oxidase inhibitors has passed the stage of being merely a pharmacological tool and is used clinically in a host of conditions to relieve pain. Although the usefulness of monamine oxidase inhibitors was first noted in the treatment of mental depression, recognition of enzyme inhibition as a general therapeutic principle lead to widespread study of application in other fields of medicine. One of the most outstanding observations concerns the beneficial results in angina pectoris with this agent.

Indications

At the international symposium on Nialamide in Lisbon, Portugal, in November 1959, scientists, and medical men from all over the world reported on the use of Nialamide for alleviation of pain in cardiovascular diseases, specially agnina pectoris, in cerebro-vascular accidents, in painful and debilitating syndromes as cancer, arthritis, neurasthenia and neuritis, in obstetric and gynaecological conditions, as an aid to anaesthesia in thoracic surgery, in the treatment of leprous reaction, in selected dermatoses, as a coadjuvant in the treatment of some allergic diseases, in metabolic craniopathy, and many neurologic depressive manifestations. Nialamide was used by us chiefly to obtain relief of pain during labour. Our study is still in its infancy and this is just a preliminary report.

Material and Method

Our trial is still in progress, but we are able to report today on 33 cases. 75 mg. (25 mg. thrice a day) orally were given to patients for about 2 weeks before the expected date of delivery. Only 20 patients took the complete treatment while in 13 others the treatment was interrupted because of irregular attendance, non-availability of Niamid tablets, and false due dates of labour given by the patients. Some of these took tablets for a short period only from 3 to 9 days before delivery, while 2 patients took tablets for as long as 22 and 35 days before delivery respectively.

According to most experiments, Nialamide produces maximum effect after 10 to 13 days of oral administration. Hence to assess our results we have had to divide our patients into two series: (1) 20 complete cases, and (2) 13 incomplete cases.

Complete cases consisted of 14 multiparas (see Table I) and 6 primiparas (see Table II). On an average these patients took three tablets, 75 mg. of Niamid orally per day, from 7 to 14 days before delivery. One took two treatments of 14 days each with an interval of 14 days and delivered 3 days after stopping the second course. Clinically it appeared that postmaturity had set in, but the baby weighed only 6 lbs. 4 ozs. Another patient took 75 mg. for 24 days and a third for 28 days. It can be seen that in all these cases the duration of the first stage is not much affected, but that of the 2nd appears to be much reduced ranging from 3 to 13 minutes. Of the 14 cases only in one did the 2nd stage last 30 minutes and in another 1½ hours. The 3rd stage was within normal limits. The weight of babies varied from 5 lbs. 5 ozs. to 7 lbs. 10 ozs. Only two cases had slight p.p.h. No sedation of any kind was given to these patients. Five patients definitely stated that the pains during labour were much less this time and 9 stated that it was slightly less than in previous labours. Pain is a subjective symptom and as we had no other means of testing sensitivity to pain, we have therefore recorded only their appreciation of labour pains after treatment with Niamid as compared to their previous labours.

TABLE I

Complete Cases — Multiparas

S. No.	Parity	Duration of treatment in days	Duration of Stages of labour I (hrs.)	II (mins.)	III (mins.)	Wt. of the baby lbs. oz.	Less pain than in previous labour	Sedation during labour
1	III	8	10¾	10	8	7-0	Yes	Nil
2	V	7	9¼	10	5	6-8	Yes	Nil
39	V	8	5¼	5	10	6-6	Yes	Nil
5	II	12	3½	3	14	7-8	—	Nil
6	II	7	6¼	5	10	6-0	—	Nil
11	II	7	3½	13	10	6-11	Yes	Nil
16	VII	24	7¼	5	10	6-8	—	Nil
17	II	11	7¼	5	10	7-10	—	Nil
20	II	14 (twice) Plus 3	7	5	10	6-4	—	Nil
30	III	28	8¼	10	10	6-7	Yes	Nil
32	II	6	?	?	10	7-0	—	Nil
33	II	12	?	30	10	6-2	—	Nil
36	IV	7	8	90	7	6-6	—	Nil
37	II	9	?	5	10	5-5	—	Nil

There were 6 primiparas (see Table II). The duration of treatment with oral Niamid, 75 mg. per day ranged from 7 to 21 days. Only one had the tablets for 30 days. Again

TABLE II

Complete Cases — Primiparas

S. No.	Duration of treatment in days	Duration of Stages of Labour I (hrs.)	II (mins.)	III (mins.)	Wt. of the baby (Lbs.-ozs.)	Sedation during labour
3	21	8½	10	5	5-11	Nil
4	9	6¾	75	15	6-6	Nil
10	7	Combined 1st & 2nd stage: 1½ hrs.		10	4-0	Nil
15	10	28	75	6	7-14	Inj. Pethidine 100 mg. when CX 3 fingers.
22	30	16½	225	MRP	5-14	Inj. Pethidine 100 mg. early in 1st stage.
26	7	16	110	10	7-4	Nil

clinically this case appeared to be postmature. She had an internal podalic version and a manual removal of placenta, but the baby weighed only 5 lbs. 14 ozs. Only in two cases was second stage specially shortened. In 1 it lasted 10 minutes and in the other the combined 1st and 2nd stages lasted 1½ hours. The weight of the babies ranged from 4 lbs. to 7 lbs. 14 ozs. Only 2 to 6 cases asked for 100 mg. Pethidine Hydrochloride for relief of pain. In the other 4 no sedatives were necessary.

Incomplete cases: There were 13 cases in this group: (see Table III)

TABLE III

Incomplete Cases

S. No.	Parity	Interval between treatment and delivery	Duration of treatment in days	Duration of stages of labour I (hrs.)	II (mins.)	III (mins.)	Wt. of the baby lbs. oz.	Less pain than in previous labour	Sedation during labour
7	I	16	14	3	150	10	6-12	/-	Nil
13	V	9	22	3	15	10	7-2	—	Nil
14	V	9	7	13½	35	10	7-4	Yes	Nil
18	V	—	4	4½	4	16	6-6	—	Nil
21	I	—	5	7½	36	9	6-4	—	Nil
25	II	4	7	4½	10	15	6-10	—	Nil
34	I	7	14	?	?	15	4-10	—	Nil
35	III	9	14	4½	5	9	5-0	Yes	Nil
9	V	25	7	3½	10	10	6-2	—	Nil
29	VIII	6	35	5¾	5	10	7-0	—	Nil
19	III	7	7	5½	3	12	5-10	—	Nil
27	IX	—	3	5	10	5	5-8	—	Nil
38	IV	3	14	11¾	10	10	5-2	—	Nil

3 primiparas and 13 multiparas. Eight of them received Niamid from 7 to 14 days and 3 from 3 to 5 days, 1 patient for 22 days and another for 35 days. For Niamid to be effective in reducing pain during labour it should be given for exactly 15 days prior to the due date, and it should be so timed that labour starts immediately after stopping the drug. Chiefly because of improper calculation of the due date of labour, these cases had an interval ranging from 3 to 16 days before the onset of labour and one of 25 days. Hence they are grouped as incomplete cases and we lost valuable clinical material. In this series also the first stage of labour was not much affected, except for one primipara where it lasted only 3 hours. In most of them the second stage was markedly shortened, viz. from 3 to 15 minutes. In a 5th para the 2nd stage lasted 36 minutes and she complained of profuse perspiration. But this case was quite definite that she had much less pain this time than before. The 3rd stage was normal. Weight of the babies ranged from 4 lbs. 10 ozs. to 7 lbs. 4 ozs. Only one patient had slight p.p.h.

2 cases out of the 13 stated with great emphasis that the pain was much less during this labour than before, and the others were indefinite. None of these patients however, including the primiparas, received any sedation during labour.

Nailamide has been conclusively proved to reduce postnatal depression, but with our class of poor patients who have hardly any education it was impossible for us to assess this factor. All we can say is that all the 33 cases seemed happy and cheerful. Because of the simplicity of the administration, the low cost and gratifying results we recommend it for trial as a useful means for the relief of pain in labour. Good results have been reported by using Nialamide in hyperemesis gravidarum, but we have not tried this.

Use of Nialamide in Gynaecology

We have tried it only in cases of primary intrinsic dysmenorrhoea. It is still in the experimental stage. We administer 75 mg. per day orally for 3 weeks before expected date of menses. We tried it in 11 cases so far. It is so difficult to have a follow-up-with our patients and most of them had it only for one month. One case stated that she had absolutely no pain after the tablets. 3 patients are expected still to report. 4 cases did not report after the tablets. In one there was no improvement. In two others the improvement was slight. Hence only 1 was completely relieved and 2 others had partial relief. We are still trying nialamide in postmenopausal psychic disturbances, but the cases are too few to report.

Conclusion

When 75 mg. per day of Nialamide (Niamid) are given orally for 10 to 15 days before onset of labour, it appears to considerably relieve pain during labour. Of the 20 complete cases only 2 primiparas needed injection pethidine hydrochlor. 100 mg. for sedation; 5 patients stated definitely that the pain was much less and 13 were delivered without sedation. Of the 13 incomplete cases two stated definitely that pain was much less but none of them received any sedation at all.

2. Niamid seemed to shorten considerably the 2nd stage of labour, both in primipara and multipara. If this is proved in a larger series of cases, it will be a great boon to parturient women.

3. In 2 cases because of improper calculation of due date of labour the drug was taken from 30 to 31 days. Clinically they appeared to go into postmaturity. But the babies were not excessively big. Neither mother nor baby suffered any bad effect.

4. All babies born to mothers who had received Niamid showed no untoward effect. They breathed and cried spontaneously after birth and were quite normal in the post-natal period.

5. The number of cases is indeed few, 33 in all, and pain being such a subjective symptom it varies with individual threshold. The results however are very gratifying. Since it is so simple to administer Niamid orally with no bad effects, we are much encouraged to try the drug in a larger series.

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