NIALAMIDE

A STUDY OF ITS EFFECT ON PAIN AND DEPRESSION

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The biochemical aspect of metabolism is principally one of enzymic activity, and an understanding in that direction holds out distinct promise in the elucidation of many problems in diseases. Because of the lack of a comprehensive picture of the total enzymic interrelationship in the present state of inadequacy of our knowledge, clinical observation has still an important place in the study of its probable implication. The use of enzyme inhibitors clinically is important in that apart from any therapeutic benefit that may follow, the effects arisen from the inhibitition may assist in the unravelling of the enzymic puzzle. This does not imply that therapeutic benefit is of lesser importance, for a doctor's primary desire is distinct from a pure scientist in that he seeks to cure and to relieve, and even in the pursuit of knowledge, his basic concept must caution him from becoming a student of pure science too readily. An attitude like this will no doubt hamper his progress by his reluctance to initiate unwarranted human experiments which may help to increase his knowledge at a greatly enhanced pace were he able to forget his primary objective.

Nialamide—a mono-amine oxidase inhibitor —has been favourably reported by workers on the field in the control of pain and depression and relatively negligible toxic effects have been noted, amongst which may be mentioned constipation, dryness of mouth, insomnia, euphoria, impotence, weakness, loss of appetite, urinary disturbance, hypotension, headache and giddiness. On the other hand, averse results on the inconsistent therapeutic value of some amine oxidase inhibitors have also been reported especially in the field of cardiac pain, and its toxic effect on the liver.

For the last 6 months a study of the effect of Nialamide on pain and exogenous depression was done in the Singapore General Hospital purely to assess its value on these conditions from a clinical standpoint.

METHOD

(a) Depression: 7 cases of exogenous depression were selected for therapeutic trial. The cause of the depression in all cases was apparent; and mentally, the patients were all orientated but unhappy and retarded.

The cases were all observed as inpatients, and subjective responses were elicited by direct leading questions. This is not such a harmful technique to adopt as it sounds, for in depressive cases, unlike psychoneurotics and functional disorders, leading questions do not tend to influence the answers.

Objectively, their general activity, attitude, and mood were observed; and at discharge, reports were obtained about their working capacity, and their adaptability in their homes.

The results were put as good if the patients became quite normal and required no medicine or treatment apart from Nialamide as maintenance. They were classified as moderate if the patients appeared better subjectively or objectively but did not recover their normal status. When no apparent benefit was obtained, the response was recorded as nil. Daily examination of blood, urine, and blood pressure was done in all cases beginning on the day before Nialamide was given, and continued on for 1 week after Nialamide was stopped. When a case was on maintenance dose, these examinations were done weekly from the third week onwards.

(b) Pains: In our clinic, we have a number of stabilised cases of cardiac pains, almost all of them had evidence of cardiac infarction some time or other. They are on one or other coronary dilators varying from Peritrate, Erythritol tetranitrate to glyceryl trinitrate. In 1959, a study of the effect of Iproniazid was done by substitution, and it was found that the beneficial effect was on the whole inferior to the standard drugs in use, but there were the occasional cases who appeared to prefer it to others.

These cases were known to us in that they were able to give a good account of their exercise capability, their frequency of pains, and their relief with treatment, and it became quite an easy matter to test their response to drugs by substitution.

Results were recorded as good if the pains were abolished and the patient was not dependent anymore on any of the drugs he used to have; moderate if the frequency or severity of pain was reduced and the patient resorted to the former drugs only from time to time;

and nil if everything remained unchanged as if Nialamide had not been given.

Two non-cardiac cases with painful conditions were also treated. One had polyarteritis nodosa for 2 years and in spite of steroids, developed extremely painful leg ulcers requiring daily pethidine injections and local anaesthetic dressings. The other was a case of inoperable carcinoma of the fundus of the stomach with severe pains.

ANALYSIS OF RESULTS

It can be seen that in painful conditions, the responses were satisfactory; for apart from the case of cancer, all of them had favourable results. The response was evident within 1 or 2 days. Serial electrocardiographic tracings showed no change, and the pulse rate, heart size and exercise response remained the same although the pains were improved or abolished. This would suggest that the benefit was not due to any direct effect on the cardiac muscle or coronary circulation but might be on the perceptive side of pain sensations. In the case of gastric cancer, she was feeling better with less pains, and was able to go without narcotics after 2 days, but on the 10th day, she suddenly developed a severe gastric haemorrhage for the first time of her illness, and was severely shocked, and had to be given blood transfusion. Whether Nialamide has any local effect on the gastric mucosa remains to be elucidated, but it has been found that no demonstrable defect in bleeding and clotting mechanism was apparent in that case, and the occurrence of the haemorrhage was probably fortuitous.

In the cases of exogenous depression, the results appeared less favourable, although the many reports from other workers had been optimistic. Apart from three cases in this series all the rest did not benefit at all. Even in the three cases, the responses were slight and of little therapeutic significance. In case 13, the patient developed an acute schizophrenic reaction on the 7th day. This has been observed in our other cases of depressive, when the depression was improved, and the causes remained operative. It would appear that depression might constitute a mental defence mechanism which might not be removed without risk, and a combination of tranquillisers with anti-depressive agents might be preferable to the latter alone. It should be pointed out that the treatment was of short duration only up to 2 weeks, and the possibility of benefit after longer treatment was not ruled out.

TOXIC EFFECTS

No serious toxic effect was seen in all cases. In 2 cases, urobilin appeared in significant quantities in urine, and no evidence of haemolysis was observed. In another, the serum bilirubin was increased, but the change was within limits of experimental error. In yet another the alkaline phosphatase went up for the duration of the treatment. These would seem to suggest that possible liver toxicity existed. Cases of hepatic necrosis had been reported in animals and in man in the use of Iproniazid, and it was not improbable that Nialamide was not exempt. 4 cases were given a week of Nialamide orally (150 mgm to 300 mgm a day) and the liver functions were examined before, at the conclusion of treatment, and 1 week after the test. Unfortunately, 2 cases refused to continue, and absconded. This unfortunately is a common problem in clinical studies in Singapore, and long term studies are on this account fraught with difficulties.

In the other two cases, both with cardiac failure, and having no jaundice and no evidence of liver deficiency, Nialamide was given in bigger doses than was recommended—300 mgm a day for one week—and daily examination was carried out so that the treatment could be interrupted at the first sign of any significant toxicity. The liver function was done before treatment, repeated after one week of treatment, and then repeated after the treatment was taken off for one week. Subjectively, the two cases felt better, and clinically, the cardiac decompensation improved in that the oedema, pulse rate, and exercise tolerance showed improvement, although the total clinical gain was no more than what one would expect from the routine management of cardiac failures. Other than the rapid onset of subjective well-being, the use of Nialamide did not seem to hasten the improvement.

However, a scrutiny of the laboratory investigations showed that in both cases, there was evidence to suggest possible toxic effect on the liver, and in the second case, occult blood appeared in the stool. The surprising feature was a definite rise in the serum albumin. The significance of the presence of occult blood and the rise of serum albumin is now under study, but as far as these two cases were concerned, toxicity to the liver seemed to be present, but reversible. This would suggest that dosage

TABLE I

No.	Race	Sex	Age	Diagnosis	Duration of illness before treatment	Complaints	Symptoms	Signs	Treatment received and duration	State before Nialamide	Nialamide	Response	Remarks
1	Chinese	M	53	Hypertension Coronary Ischaemia	4 weeks	Retrosternal pain	Effort angina +++	ECG-T inverted AVL. ST elevated V3. BP 230/140 Grade I fundus Heart not enlarged. No failure	Ansolysen Chlorothiazide Serpasil Gylceryl trinitrate 1 p.r.n. 4 weeks on Peritrate	Rest in bed Requires trinitrate at least once a day. BP 140/80 Angina ++	1 b.d. 1 week. 1 t.i.d. 1 week. No peritrate. or gly. Trin.	Moderate Angina free next day ,, remained so after Nialamide. BP 120/150 / 80/90 Hb. — WBC — RBC — Platelets Urine nad. ECG same.	No toxic effect. Good response
2	Indian	M	84	Hypertension Coronary Thrombosis Tropical Eosinophilia	7 years Hypertension C.T. 2 months	Dyspnoea on effort ++	Dyspnoea effort Asthma	ECG-QS II, III, AVR, AVF. X-ray E.L.	Serpasil, Apresoline, Ansolysen.	Apathetic. In bed all day. BP 140/90 Hb. 94% WBC 10,200 Platelet 90,000.	1 b.d. 1 week.	Good active 140/80 150 Hb. 84% WBC 6,400 Platelet 65,000 6th day.	Good effect on blood liver ? due to Tropical Eosinophilia
3	Chinese	F	34	Polyarteritis with painful ulcer	3 years	Painful ulcers off and on. Worse 1 week	Painful ulcers	Ulcers feet BP 140/90	Largactil 2 weeks Prednisolone 2 years Inj. Pethid. daily 1 week Dressing.	Groaning with pain Requires daily 1-2 Pethidine BP 140/90	1 b.d. 1 week.	Good. No Pethidine 2 days. BP 130/90 Urobilin trace No change in blood.	? effect on ulcer.

No.	Race	Sex	Age	Diagnosis	Duration of illness before treatment	Complaints	Symptoms	Signs	Treatment received and duration	State before Nialamide	Nialamide	Response	Remarks
4	Eurasian	F	68	Depression Diabetes Hypertension	4 years weakness 4 weeks gross disability	Very weak	Unable to walk or wash. Unable to sleep.	BP 220/120 Diabetes Depressed Tearful	Rastinon 1 o.m. Nicotinic acid 100 mg t.i.d. Multivite 1 t.i.d. Serpasil 1 t.i.d. Dexedrine ½ Tab o.m.	Tearful Insomnia BP 220/120	1 b.d. 1 week.	No change BP 150-240 / 90-110 No change in blood and urine	No change
5	Chinese	F	48	Angina	5 days Previous attack 15 years ago	Chest pain	Chest pain on exertion. Palpitation.	BP 120/80 ECG low voltage AVL Std. I	—	Unable to work or exercise	1 o.m. 1 week.	120/80 No pain from 2nd day. ECG same good.	--
6	Indian	M	39	Mitral stenosis Chest pain	Mitral stenosis 29 years 4 months	Chest pain	Chest pain on exertion ECG normal	BP 120/80 Pain on walking	Peritrate Bellergal 1 t.i.d. Largactil 1 o.m.	Bed-ridden	1 o.m. 2 weeks.	BP 100/70 ECG No change. No change in blood, marrow or urine.	—
7	Malay	M	30	Palpitation and pain in legs & arms. Depressed	10 months	Palpitation	ECG-NAD Pain in legs & chest Depressed	BP 120/80 Depressed Bedridden	Miltown Serpasil Peritrate. Gylceryl trinitrate Dispirin	Bed-ridden	1 b.d. 1 week.	BP 120/80 Moderate 2nd day No toxic effect	
8	Indian	M	47	Coronary thrombosis and angina	Coronary thrombosis 2 years Angina 2 years	Angina of effort ++	--	ECG Post. lat. infarct BP 110/80 Heart enlarged	Choledyl Peritrate Digitalis Iproniazid	Effort Angina + working	1 b.d. 1 t.i.d. Response in 2 days	Moderate Angina + Can go without Peritrate and Iproniazid	— No toxic efects.

No.	Race	Sex	Age	Diagnosis	Duration of illness before treatment	Complaints	Symptoms	Signs	Treatment received and duration	State before Nialamide	Nialamide	Response	Remarks
9	Chinese	F	49	Depression	Acute Co. for 4 days, illness for several years	—	—	Depressed unable to work	—	—	1 t.i.d. Response in 4 days	Go back to work Moderate	No toxic effect.
10	Chinese	F	32	Thyrotoxicosis Depression + headache	Thyroid trouble for 1 year Headache 1 year	—	—	Depressed and incapacitated BP 120/70	—	—	1 t.i.d. BP 110/70	No change	No toxic effect.
11	Malay	F	36	Carcinoma stomach Pain on swallowing	Dysphagia, no appetite 1 month	—	—	No cause locally	—	—	1 t.i.d. BP 110/80 or 100/80	No change	Collapsed after 1 week due to gastric bleeding. Given blood transfusion. Nialamide discontinued. ? effect ? coincidence
12	Chinese	F	67	Fever Depression	P.U.O. 3 days Depression ? duration	—	—	Inactive non-responsive	—	No evidence of cerebral involvement.	1 t.i.d.	No change	No change or toxicity.
13	Chinese	F	39	Depression	2 months	—	—	Depression.	—	—	1 t.i.d.	Better after 2 days became aggressive on 10th. day.	

TABLE II

Cardiac Pain

Case No.	Duration of treatment	Latent Period	Response
1	2 weeks	1 day	Moderate
2	1 week	1 day	Good
5	1 week	2 days	Good
8	2 weeks	2 days	Moderate

Other Pains

Case No.	Duration of treatment	Latent Period	Response
3 Polyarteritis	1 week	2 days	Good
11 Ca. Stomach	1 week	—	Nil

TABLE III

Depression

Case No.	Duration of treatment	Latent Period	Response
4	1 week	—	Nil
6	2 weeks	—	Nil
7	1 week	Unknown	Moderate
9	1 week	4 days	Moderate
10	1 week	—	Nil
12	1 week	—	Nil
13	1 week	2 days	Initial response

TABLE IV

Response

Case No.	Subjective	Objective	Duration
1	++	—	Lasting
2	+++	— (No coronary dilator required)	Lasting
3	+++	++ (go without analgesic)	Lasting
4	—	—	—
5	+++	— (No coronary dilator required)	Lasting
6	—	—	—
7	+	—	—
8	+	++ (patient accepted substitute for Iproniazid)	During treatment only
9	++	++	Lasting
10	—	—	—
11	—	—	—
12	—	—	—
13	++	—	Transient

TABLE V

Toxicity

Case No.	B.P.	Blood	Liver	Urine
1	—	—	—	—
2	—	—	—	Urobilin in urine +
3	—	—	—	Urobilin trace
4	—	—	—	—
5	—	—	—	—
6	—	—	—	—
7	—	—	—	—
8	—	—	—	—
9	—	—	Alkaline phosphatase up	—
10	—	—	—	—
11	—	—	Thymol turbidity 2 — 3 units (Collapsed due to gastric bleeding)	—
12	—	—	—	—
13	—	—	—	—

TABLE VI

	Serum Protein	Serum Albumin	Serum Globulin	Serum bilirubin	Thymol turbidity	Alkaline Phosphatase	Urine urobilinogen	Occult blood in Stool
I. Before	7.42	3.74	3.68	0.5	3	8	—	—
1 week on Nialamide	7.94	4.45	3.49	0.25	4	8	+	—
1 week after Nialamide was off	7.38	4.30	3.08	0.10	4	8	—	—
II. Before	7.40	3.90	3.49	0.25	3	8	—	—
1 week on Nialamide	7.96	4.61	3.35	0.40	7	12	+	+
1 week after Nialamide was off	7.38	4.30	3.08	0.15	3	8	—	—

TABLE VII

Intravenous Nialamide

Case No.	Diagnosis	Nialamide Dosage	Results on patient	Liver Function test* Evidence of impairment
1	Depression	100 mg I.V. thrice a week x 3	Nil	Absent
2	Depression	100 mg I.V. every 2 days x 4	Nil	Absent
3	Depression	100 mg I.V. daily x 7	Moderate	Absent
4	Cancer of Stomach with pain	100 mg I.V. daily x 7	Nil	Absent
5	Depression	100 mg I.V. daily x 7	Nil	Absent
6	Depression	100 mg I.V. daily x 7	Nil	Absent

*The same range of tests was done as in Table VI.

exceeding 150 mgm a day might not be advisable, and also that a careful observation of liver toxicity had to be made in cases with long term therapy.

Subsequently parenteral Nialamide was available, and a few cases of exogenous depressives were selected for treatment to see if large doses would benefit the depression, and also the liver toxicity if indeed present would become more evident. In the first two cases 100 mgm Nialamide was given intravenously every third day for 7 doses, and the patient was observed for the clinical response, and also the effect on the liver function. As no obvious deleterious effect was seen, 4 subsequent cases were given the same dose daily for 7 days.

RESULTS AND DISCUSSION

Apart from 1 case, there was no significant change in the depression observed. This was quite in keeping with the results obtained when oral therapy was given. However, the liver function tests showed no changes of significance, nor was the change in serum albumen observed. As the dose given was now of a greater magnitude compared to the oral dose, the inference must be that the fear of immediate toxicity on the liver was not substantiated unless there could be demonstrated a difference of effect between oral and intravenous therapy.

SUMMARY

Nialamide was found to be of value in the relief of pain in a variety of situations such as angina pectoris ischaemic ulceration, gastric cancer. The oral therapy produced some changes in liver function tests which would warrant further study. On the other hand, intravenous treatment with large doses did not produce any evidence of liver toxicity.