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TREATMENT OF INTRACTABLE PAIN WITH LARGE DOSES OF MORPHINE AND DIAMINO-PHENYLTHIAZOLE

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Morphine given as its salts has the world-wide reputation of being the most effective agent for the relief of pain and associated mental anguish. Its use in large doses for the relief of severe pain, of either medical or surgical origin, has been hindered by the risk of producing severe respiratory depression.

To date, the only substances known clinically to be active in combating this respiratory depressant effect have been N-allylnormorphine ("lethidrone," "nalorphine," "nalline") and, more recently, levallorphan (Eckenhoff and Funderberg, 1954). Lasagna and Beecher (1954) have studied the analgesic potentialities of mixtures of morphine and nalorphine, but, to date, no satisfactory clinical combination of these two drugs has been found that, in adequate therapeutic doses, does not produce some toxic effect.

In this paper we wish to discuss the clinical use, in 35 cases, of a morphine antagonist—namely, 2:4-diamino-5-phenylthiazole hydrobromide (D.A.P.T.) (Davies *et al.*, 1950)—which, while having in therapeutic doses little effect on the analgesic properties of morphine, reveals marked and lasting antagonism to its respiratory depressant effect and thus renders the clinical use of large doses of morphine a safe procedure.

The use of D.A.P.T. as a morphine antagonist in animals has been previously reported (Shaw and Bentley, 1949, 1952; Shaw and Shulman, 1955), and D.A.P.T. has also been used as a synergist with $\beta\beta$ -methylethylglutarimide (NP13, "megimide") in the treatment of barbiturate intoxication (Shulman *et al.*, 1955).

Pharmacology of D.A.P.T.

From the above animal experiments and from the clinical results obtained it would appear that the following are the facts of pharmacological importance regarding D.A.P.T.

1. It is a specific antagonist of morphine (Shaw and Bentley, 1955). It has been found to be specially effective in relieving the respiratory depression caused by excessive

doses of morphine, heroin, "omnupon," and the synthetic analgesics, pethidine, and methadone hydrochloride. The depth of respiration is increased rather than the rate. It appears sometimes to antagonize the vomiting and, usually, the constipation associated with morphine.

2. It appears to be a non-specific respiratory stimulant, especially by the parenteral route. Its use in barbiturate poisoning has been discussed already (Shulman *et al.*, 1955).

3. Prolonged administration of large doses of morphine—1½–2 gr. (80–130 mg.) thrice daily—in the presence of D.A.P.T. demonstrated that these doses did not lose their analgesic effect—or, at the most, the morphine dosage had to be increased by 30%. We feel it would be unwise on this evidence to claim that D.A.P.T. prevents the onset of tolerance, but in our series (30 cases continuing, some up to five months) there were no signs of development of tolerance or addiction. In two cases the injection of large—2-gr. (130-mg.)—doses of morphine thrice daily enabled us to reduce the total daily requirement when this had been given in small—½-gr. (32-mg.)—amounts at frequent intervals.

4. Whereas therapeutic doses will antagonize the respiratory depressant effect of morphine, an increase in the dosage will also antagonize its soporific action. A still higher dosage may leave the patient awake and mentally restless. This may be associated with transient muscular twitches, prolonged and forced expirations, and occasionally vomiting. Mental disorientation has been produced occasionally in the aged.

5. It seems to have a high therapeutic index (about 10) when used in animals or clinically, either as a morphine antagonist or as a synergist to $\beta\beta$ -methylethylglutarimide in the treatment of barbiturate intoxication. In the latter case doses of more than 0.5 g. have been given over a two-hour period with the production of neither acute nor delayed toxic symptoms.

6. It has no analgesic properties of its own when given by either the oral or the parenteral route.

7. Small doses have little effect on the blood pressure, but with a large intravenous dose (75 mg.) there may be a rise in blood pressure.

8. It is a stable white crystalline powder readily soluble in water (4%) at room temperature. Physiological solutions slowly hydrolyse, but refrigerated solutions have been shown to retain their activity for periods up to one week.

Some preparations of D.A.P.T. contain a toxic impurity, and it has been our practice to check all samples for toxicity by means of a "rat test"—that is, the LD₅₀ of a standard pure sample is compared with that of the new preparation.

Treatment of Severe Pain

Principle.—Before the new treatment can be successfully applied it is essential to discard an ancient concept—namely, that morphine is a dangerous drug. Up till now the use of morphine has been attended by the immediate risk of respiratory depression and the long-term inconvenience of tolerance. Both these dangers are now banished by the use of the thiazole derivative. Accordingly it is recommended that the present practice of the administration of small dosages of morphine at frequent intervals be abandoned. One should aim at large—1–2-gr. (65–130-mg.)—doses of morphine, which are sufficient to produce an analgesia of six to eight hours' duration and which nevertheless still keep the patient alert. These doses should be given at the initiation of the treatment. The great psychological advantage of never having the patient suffer severe pain cannot be too strongly stressed. The principle of the treatment therefore consists in giving gradually increasing amounts—½-gr. (16-mg.) increments—of morphine accompanied by D.A.P.T. (15 mg.) over a period of one (or two) days until the desired degree of analgesia is obtained.

Detail.—The patient will probably be receiving ½–¾ gr. (16–22 mg.) of morphine. In the following, "treatment" means the injection of both morphine and D.A.P.T. and

the subsequent observations of respiration, etc. Inject $\frac{1}{2}$ gr. (32 mg.) of morphine, and 15 mg. of D.A.P.T. 30 minutes later—that is, when the maximum effect of morphine is being exerted—both injections being intramuscular. Observe respirations (and sedation) every 15 minutes for two hours. If the pain returns before the termination of six hours and the respirations have not fallen below 6–8 a minute, repeat the “treatment” with $\frac{1}{2}$ gr. (50 g.) of morphine and 15 mg. of D.A.P.T. (observe respirations as before). If the degree of respiratory depression should cause concern a dose of 10 mg. of D.A.P.T. may be repeated at 10-minute intervals (see Note 3). If the pain returns before the expiration of six hours, and the respirations have not fallen below 6–8 a minute, repeat the “treatment” with 1 gr. (65 mg.) of morphine and 15 mg. of D.A.P.T. (observe respiration as before).

At this stage pain of mild-to-moderate intensity should be receiving up to eight hours' relief per “treatment” without any undue sedation. The patient is now said to be stabilized.

In cases of very severe pain it may be necessary to give doses of morphine of up to 2 gr. (130 mg.) three or four times a day, in the following manner.

Inject $1\frac{1}{2}$ gr. (90 mg.) of morphine and 15 mg. of D.A.P.T. (intramuscularly) and observe respiration, etc., as before. Repeat this “treatment” when pain returns or at the end of six hours. If the analgesia is still inadequate and the respirations have not fallen below 6–8 a minute give two “treatments” of $1\frac{1}{2}$ gr. (100 mg.) of morphine and 15 mg. of D.A.P.T. If adequate analgesia is not obtained inject 2 gr. (130 mg.) of morphine and 15 mg. of D.A.P.T. When the patient has been stabilized, usually on the second day of treatment, the intramuscular injection of D.A.P.T. is replaced by the oral administration. A dose of 20 mg. (one tablet) of D.A.P.T. is given at the same time as the morphine injection. If the patient is unduly sedated during the day, the oral dose of D.A.P.T. may be increased up to 30 or 40 mg., and reduced to 20 mg. at night.

Notes

1. The plan of the procedure is simple. The patient is given graded doses of morphine (with D.A.P.T.) until respiratory depression (or sedation) is evident or an analgesia of from six to eight hours is obtained.

2. D.A.P.T. is an extremely safe drug. The dose is 15 mg. intramuscularly; as much as 100 mg. has been given without ill effect, but careful administration is advised as these high doses are approached.

3. Slow and irregular breathing is not a sign of respiratory danger, provided that the respirations are deep and cyanosis is not present. Under these conditions a rate as slow as 6 a minute is not dangerous. If at any time the respiration of the patient should cause concern—that is, if the rate should fall below 6–8 or the breathing be shallow, with cyanosis—further intramuscular injections of 10 mg. of D.A.P.T. may be made at 10-minute intervals until 60 mg. of D.A.P.T. has been given. It must be stressed that

D.A.P.T. will increase the depth rather than the rate of respiration. For more rapid action the D.A.P.T. may be injected intravenously.

4. It has been found easier to prevent the onset of pain than to alleviate it once it has occurred. Accordingly it is better to give four treatments a day rather than three if pain tends to recur at about seven hours.

5. Care should always be exercised in the treatment of the aged.

6. At night it is desirable to give a barbiturate cover or an injection of hyoscine—1/150–1/100 gr. (0.43–0.65 mg.).

7. If the patient has not received sufficient relief from a large injection (over 1 gr.—65 mg.) of morphine it is safe to repeat the injection (with D.A.P.T.) at any time after two hours.

8. If the patient's condition worsens as death approaches and the period of analgesia shortens, the dose of morphine may be increased by $\frac{1}{2}$ -gr. (16-mg.) increments. The need to increase the D.A.P.T. is unusual, but it may be increased by 5–10 mg. in the presence of respiratory depression or undue sedation.

9. D.A.P.T. given in therapeutic doses to a morphinized patient causes practically no side-effects. Slight irregular flickers of the fingers, shoulder, and neck were occasionally observed, but these could not be differentiated from identical movements seen in the drowsy and deeply morphinized patient to whom no D.A.P.T. had been given.

In some of our early cases morphine and thiazole were given cautiously by continuous intravenous therapy. Such procedure has not been necessary in our later cases.

The Concomitant Use of Other Drugs

There are no pharmacological contraindications to the use of the following drugs with D.A.P.T.

1. Hyoscine.—This drug in larger doses (1/100 gr. (0.65 mg.) intramuscularly) increases the drowsiness and may extend the period of analgesia. It should be used only at night or in cases of very severe pain.

2. Atropine has a similar action to that of hyoscine, but less marked.

3. Barbiturate.—This drug may be used where it is felt to be of benefit, especially at night if sleep does not come easily.

4. Chlorpromazine (“Largactil”).—This drug has been used in about 10 of our cases. Vomiting is usually lessened and the period of analgesia increased, but the patient is much drowsier.

5. “Marzine.”—This new anti-emetic has been used in six cases of hyperemesis. The vomiting is usually prevented until the terminal stages are reached, when it appears to lose its efficacy.

A brief synopsis of two of the 35 cases investigated appears below. Further summaries are given in Table I. A list of the dosages required for complete relief is given in Table II. In all but four cases these dosages remained unaltered until death supervened. In the four cases mentioned—dose 1– $1\frac{1}{2}$ gr. (65–80 mg.)—the dose had to be increased to 2 gr. (130 mg.) during the final two days.

TABLE I

Age and Sex (Years)	Condition	Before Treatment		Treatment		After Treatment Duration of Analgesia (Hours)	Duration of Treatment (Weeks)	Comments
		Dose of Morphine gr. mg.	Duration of Analgesia (Hours)	Morphine (gr.)	D.A.P.T. (mg.)			
F 35	Ca. breast, oedema arm	$\frac{1}{2}$ 22	2–3	2 I.M. q.d.	20–40 P.O.	6	18	Excellent relief of pain. No side-effects with large dose morphine over 4 months' period
F 42	Ca. cervix	$\frac{1}{2}$ 22	2–4	1 I.M.	8 I.M.	8–12	2	
F 69	Melanoma of toe	$\frac{1}{2}$ 16	2	1 I.M. b.d.	8 I.M.	8–12	2	
F 65	Ca. breast, oedema left arm	$\frac{1}{2}$ 16	2	$\frac{1}{2}$ I.M. q.d.	20 P.O.	6–7	4	Slight mental disorientation due to secondary in brain or to morphine (?)
F 55	Ca. breast	$\frac{1}{2}$ 22	1 $\frac{1}{2}$	1 I.M. t.i.d.	20 I.M.	8	1	
F 55	„ femur	$\frac{1}{2}$ 32	2	1 I.M. t.i.d. 2 I.M. (terminal two days)	20 P.O.	8	12	Complete relief from severe pain. No side-effects
F 85	Gangrene left foot	$\frac{1}{2}$ 11	2–4	1 I.V. 1 I.M.	6 I.V. 4 I.M.	10–12 6–10	2	8 mg. D.A.P.T. gave signs of mental disorientation in old patient
F 52	Ca. colon	$\frac{1}{2}$ 32	2	2 I.M. q.d.	20–40 P.O.	6–7	10	Slight double vision due to large dose of morphine
F 78	„ breast	$\frac{1}{2}$ 16	1	$\frac{1}{2}$ I.M. t.i.d.	20 P.O.	8	13	No mental disorientation
F 55	„ femur	$\frac{1}{2}$ 16	2	1 I.M. t.i.d.	40 P.O. (day); 20 P.O. (night)	8	12	Hospitalized at commencement. One month later returned home

TABLE II

Dose of Morphine to Give 8 Hours' Analgesia	No. of Patients Receiving Relief
$\frac{1}{4}$ gr. (32 mg.)	2
$\frac{1}{2}$ " (48 ")	3
1 " (65 ")	8
$1\frac{1}{2}$ " (77 ")	10
$1\frac{3}{4}$ " (110 ")	6
2 " (130 ")	5
$2\frac{1}{2}$ " (160 ")	1
	35

Case 1.—A woman aged 52 had cancer of the lower jaw with extensive metastases and was greatly emaciated. When seen she was receiving 8 gr. (0.52 g.) of morphine a day, in divided doses, with less than two hours' relief from pain. Vomiting and constipation were troublesome. The patient was stabilized with $1\frac{1}{2}$ gr. (110 mg.) of morphine and 15 mg. of D.A.P.T. intramuscularly. During the next two days she was free of pain for six hours at a time and the vomiting and constipation were relieved. The dosage of morphine was then increased to 2 gr. (130 mg.) and 20 mg. of thiazole was given orally. Pain was relieved for eight hours, and she did not feel drowsy. The treatment continued for five weeks until the patient died. There were no untoward symptoms other than a transitory mild mental disorientation. This disorientation has been observed in other cases: it is mild and transitory, and appears to be due to the large doses of morphine rather than the D.A.P.T., as it has been observed only in the older patients.

Case 2.—A woman aged 38 with cancer of the breast, marked oedema of the left arm, and intolerable pain received no more than two hours' relief from $\frac{1}{4}$ gr. (16 mg.) of morphine. Treatment was begun, and the patient stabilized, on $1\frac{1}{2}$ gr. (110 mg.) of morphine and 15 mg. of D.A.P.T. intramuscularly three times a day. There was complete absence of pain with a decrease in the incidence of vomiting, and the constipation was rectified. On the fourth day oral administration of D.A.P.T. (20 mg.) was substituted for intramuscular injection. Later the dose of D.A.P.T. given during the day was increased to 40 mg. at each "treatment" to combat slight sedation (the nightly dose remained at 20 mg.). Two months later the dose of morphine had to be increased to 2 gr. (130 mg.) three times a day; it is impossible to say whether this was due to development of tolerance or the increasing severity of the pain. There were no untoward side-reactions. The patient died after 18 weeks' treatment.

At the beginning of treatment this patient was very depressed. About one week after initiation her mood changed to one of cheerfulness and remained so until within one week of death. In about one-quarter of our cases we have noticed this favourable change in outlook. It does not appear to be a euphoria due to the morphine, but rather owes its origin to the D.A.P.T. This aspect is still under investigation.

Discussion

The adequate relief of prolonged and severe pain still remains one of the unsolved problems of medicine. To date, morphine and its analogues have been the drugs used, and these have been only partially effective in producing relief from severe pain. This is due to the fact that it has not been possible to administer sufficiently large doses to produce complete analgesia without evoking dangerous and undesirable side-effects such as respiratory depression, tolerance, vomiting, and constipation; especially in old and cachectic patients with poor hepatic and renal function.

The method here described, incorporating the use of 2:4-diamino-5-phenylthiazole hydrobromide (D.A.P.T.), permits the use of large doses of morphine, adequate to effect satisfactory analgesia, without the associated production of these dangerous and undesirable side-effects.

Special mention must be made of the apparent ability of D.A.P.T. to prevent or delay the onset of tolerance. This clinical observation, if substantiated by further work in progress, would make the action of D.A.P.T. unique in this regard.

As it is rare to have the opportunity of safely administering doses of morphine of the order of 1–2 gr. (65–130 g.) in a single injection, the following few points of physiological interest arising therefrom are worthy of mention.

The slow intravenous administration (20 minutes) of 1 gr. (65 mg.) of morphine sulphate with 1/150 gr. (0.43 mg.) of hyoscine hydrobromide exerts its maximum clinical effect

within 20 minutes. Given intramuscularly, the full effect is not exerted for 40 minutes. These observations are also borne out in dogs under electroencephalographic control.

The slow intravenous or intramuscular administration of 1 gr. (65 mg.) of morphine sulphate and 1/150 gr. (0.43 mg.) of hyoscine hydrobromide usually has little depressant effect on the blood pressure or pulse rate. An occasional fall in the systolic pressure of 5–15 mm. Hg, associated with a transient pallor of the skin and a subjective feeling of cold, is sometimes observed, but this is quickly followed by a warm, flushed, and slightly sweaty skin with a return to normal blood pressure and an accompanying subjective feeling of warmth.

It would be natural to compare the action of D.A.P.T. with that of N-allylnormorphine (nalline). A full clinical comparison will be given in a later paper (Shulman, in preparation).

Nalline by itself has certain opiate properties and is not free from undesirable side-reactions when given in therapeutic doses (Payne, 1954; and several others). D.A.P.T. in doses at least five times the therapeutic is almost without side-reactions of any kind.

Nalline produces withdrawal symptoms in patients who have received only a few doses of morphine. This we have never observed with D.A.P.T. in therapeutic cases. Indeed, if it were so, our method of treatment of intolerable pain would not be possible, as all our patients had been receiving morphine before the beginning of treatment.

Nalline itself may cause vomiting, and does not appear to antagonize that due to morphine.

Nalline would appear to antagonize the analgesic action of morphine. This is certainly not the case with D.A.P.T. in therapeutic doses. Lasagna and Beecher (1954) have tried unsuccessfully to evolve a combination of nalorphine and morphine in post-operative patients and healthy volunteers which would give the desired therapeutic effect of analgesia without the concomitant production of the associated unpleasant side-reactions of morphine, and have discussed the difficulties involved in obtaining such a clinically useful mixture.

In addition to the extensive series of cases given above, D.A.P.T. has been used in a few cases of neonatal asphyxia, in methadone hydrochloride poisoning, and for the relief of post-operative pain. In the last-mentioned example the ability of the patient to cough painlessly was important. It should now be possible to use larger doses of morphine pre-operatively in conjunction with D.A.P.T., perhaps by intravenous administration. Finally, the removal of the risk of respiratory depression due to morphine should lead to an extension of this drug's use in the fields where it is already of value—namely, "shock," coronary occlusion, obstetrics, etc.—and may open up new fields in anaesthesia.

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