Treatment of Zoster with Idoxuridine in Dimethyl Sulphoxide. Results of Two Double-blind Controlled Trials

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Summary: The antiviral effect of 5% idoxuridine in dimethyl sulphoxide intermittently applied and of 40% idoxuridine in dimethyl sulphoxide continuously applied for four days to the lesions in patients with zoster of recent onset was studied in two double-blind controlled trials. Most, but not all, of the patients receiving intermittent active treatment had pain for a short period only. The effect of continuous treatment was striking: pain had disappeared within nine days in all the patients and healing was accelerated. The results were statistically significant.

Introduction

Varicella-zoster virus is a DNA virus closely related to that of herpes simplex. Idoxuridine has been shown to have an effect on the virus in vitro (Rapp and Vanderslice, 1964). In view of the satisfactory results achieved with 5% idoxuridine in dimethyl sulphoxide in the treatment of herpes simplex virus infections of the skin (MacCallum and Juel-Jensen, 1966; Juel-Jensen, 1969) it seemed desirable to test whether this treatment was also effective in zoster. The outstanding feature of zoster is pain, both at the time of the acute lesion and subsequently, and it was hoped that if it were possible to inhibit further replication of the virus at the peripheral sites of the pathological processes the consequences of the disease, and particularly the pain, might be ameliorated.

Initially a series of 25 patients (Table I) with zoster of recent onset were treated with 5% idoxuridine in dimethyl sulphoxide, which was painted on the lesion four times a day for four days. The duration of the pain, the moment when the vesicles were all dry, and the time when complete healing had taken place were noted. The clinical impression was that this treatment was beneficial, and a double-blind trial was therefore devised. This trial took place from December 1967 to September 1968. It confirmed that most patients had pain for only a short period but that a few suffered for a long time; therefore continuous application of a stronger solution of idoxuridine was tried, and in turn was subjected to a double blind trial. The trials are described below and discussed together.

Methods

The patients participating were referred by the ophthalmic surgeons in the Oxford Eye Hospital, by colleagues from the general medical and surgical services in the Radcliffe Infirmary, by the infectious disease unit, and by general practitioners in Oxford. The objects of the trial were carefully explained to each patient. Only those with vesicles of recent onset were included. If the rash was dry the patient was not admitted to the trial. A haemoglobin estimation, white blood cell count, and platelet count were done on the first occasion and after the end of treatment. Liver function tests (alkaline phosphatase and serum alanine aminotransferase (S.G.P.T.)) were performed. Immunoglobulins were assayed to exclude hypogammaglobulinaemia. Blood was taken on the first visit and on subsequent occasions for assay of varicella-zoster antibodies. Vesicle fluid was taken by capillary pipette and sent to the Virus Laboratory without delay for culture.

Three solutions had been made up in identical bottles; in the first trial 5% idoxuridine in dimethyl sulphoxide, dimethyl sulphoxide alone, and normal saline with garlic to simulate the faint smell of dimethyl sulphoxide due to allocin; in the second trial 40% idoxuridine in purified dimethyl sulphoxide, purified dimethyl sulphoxide alone, and normal saline with garlic. The patients were allotted one of the three solutions in a double-blind random fashion. In the first trial the patient was asked to apply the material four times a day for four days with a small paintbrush; in the second trial the material was applied continuously on lint, cut to cover the affected area, and rewetted daily for four days. He (or she) was seen daily initially, and subsequently at intervals frequent enough to allow records to be kept of the duration of the pain, when the vesicles were dry and flat, and when the last scab had gone and complete healing of the skin had taken place. Any alteration in the sense of touch and temperature was recorded and mapped out. Patients with ophthalmic zoster were seen concurrently by the ophthalmologists if the eye was involved. They received treatment with idoxuridine eye ointment and, if indicated, atropine drops and bacterial antimicrobial ointment to the eye.

Trial 1

In this trial 5% idoxuridine in dimethyl sulphoxide was applied intermittently. Twenty-four patients participated. It must be appreciated that some zoster patients never get pain or other altered sensation. The patients on active intermittent treatment apparently fared better than those in the control groups with regard to pain, the most troublesome feature of zoster (Table II). Though there is a suggestion that healing occurred more quickly in the actively treated group the results are not statistically significant. The uncontrolled group of 25 patients (Table I) showed similar figures, not significantly different statistically from those in the controlled actively treated group. The duration of pain did not appear to be related to sex. The average age of the lesion when the patient was first seen was of the same order: 2·9, 3·6, and 3·8 days for the three groups.

Positive virus cultures were obtained in 12 of the 24 patients (Table II). In those with negative virus cultures an initial high level or a rise in complement-fixing antibody titre was found, in some instances to 1/1,024, confirming the diagnosis. There was no suggestion that those treated with idoxuridine achieved a lower titre. In many patients the initial blood count showed a number of atypical mononuclear cells on the first occasion. In no patient was the S.G.P.T. abnormal, nor was there any drop in white blood cell or platelet count, though a few patients initially before treatment had a low count (3,000-4,000 white cells, 120,000-150,000 platelets) presumably caused by the viral disease.

Trial 2

In this trial zoster was treated wih continuously applied 40% idoxuridine in purified dimethyl sulphoxide. Though 5% idoxuridine in dimethyl sulphoxide appeared to have a

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TABLE I.—*Results of Uncontrolled Treatment of Zoster with 5% Idoxuridine in Dimethyl Sulphoxide Intermittently Applied*

Case No.	Site (Cranial or Segmental Nerve concerned)	Sex and Age	Duration before Treatment	Duration of Pain	Vesicles Dry	Scab Gone	Virus Cultures	Outlying Pocks
			Days from Start of Treatment					
1	LV[1+]	M. 65	6	5	5	34	+	
2	LV[1+], LIII, IV	M. 60	5	120	14	35	+	
3	RV[1]	F. 78	5	11	9	43	0	+
4	RC6 + motor	M. 59	5	7	7	21	0	
5	RV[1]	F. 61	4	15	4	29	+	+
6	RT9	F. 44	5	7	6	13	0	
7	RV[1-II]	M. 46	3	0	5	20	+	
8	RV[1]	F. 69	1	6	6	10	0	
9	LT5	F. 75	3	0	1	?	0	
10	RC3	F. 73	2	Demented	2	?	0	
11	RT3	M. 70	2	4+ (died)	4	Died	0	
12	RL1	F. 85	1	Demented	12	?	0	
13	RT12	F. 59	2	20	7	20	0	
14	LS2	M. 57	4	2	2	8	+	
15	LV[1]	M. 19	5	1	2	20	0	
16	LV[1]	F. 81	3	1	3	?	+	
17	LL1	M. 73	5	1	3	?	0	
18	LV[1]	F. 61	1	25	4	25	+	+
19	LV[1]	M. 35	4	0	1	?	0	
20	LT6	F. 91	1	6+ (died)	1	Died	+	
21	RV[1]	F. 43	10	0	3	12	0	
22	LV[1]	M. 54	2		No reliable record		+	
23	LT5	M. 58	6	6	5	?	0	
24	RV[1]	M. 70	5	?	4	?	+	
25	LT4	M. 60	No record	3	2	20	+	
		Mean 61·8 Median 60·5	Mean 3·8	Median 6	Median 4	Median 20	11/25	3/25

TABLE II.—*Results of a Double-blind Trial of Saline with Garlic, Dimethyl Sulphoxide, and 5% Idoxuridine in Dimethyl Sulphoxide Intermittently Applied in Treatment of Zoster*

Case No.	Site (Cranial or Segmental Nerve Concerned)	Sex and Age	Age of Lesion	Duration of Pain	Vesicles Dry	Scab Gone	Altered Sensation	Virus Isolation	Outlying Pocks	
			Days from Start of Treatment							
2	LV[1+]	F. 24	3	3	6	13	17	+	0	
6	RV[1]	F. 50	2	0	3	14	0	+	0	
9	LV[II-1]	F. 58	2	2	2	10	0	+	0	
11	LVI+	M. 65	3	3	3	60 s.a.	210	+	+	5% Idoxuridine in 100% Dimethyl Sulphoxide
18	LL1	F. 81	6	120	2	8	120	0	+	
19	LV[1]	M. 82	2	1	6	14	20	0	0	
21	RV[1+],RIII,IV,VI,VII	F. 78	2	5	5	19 s.a.	0	0	+	
		Mean 62·6 Median 65	Mean 2·9	Median 3	Median 3	Median 13	Median 70	4/7	3/7	Patients with absent pain or absent altered sensation not included in these figures
1	RV[1+]	F. 60	1	12	3	40	282	+	0	
4	LC5	M. 55	2	28	5	28	0	0	0	
10	RV[1+]	M. 70	3	80	6	18	180	0	0	
15	LV[1]	F. 77	5	15	2	15	0	+	0	100% Dimethyl Sulphoxide
17	RV[1]	F. 61	4	7	7	30	0	+	+	
20	RT8-9	F. 60	3	0	2	10	0	0	0	
22	RV[1]	F. 86	7	4	6	30	0	0	0	
		Mean 67·0 Median 61	Mean 3·6	Median 13·5	Median 5	Median 28	Median 231	3/7	1/7	
3	LV[1-II+] LIII-IV	M. 69	3	90	13	30	94	+	+	
5	LV[1+]	F. 86	2	5	2	21	90	0	0	
7	RT2	M. 59	8	(9+)	9	(9+)	(9+)	0	0	
					Moved away					
8	RV[1+]	F. 64	7	30	9	30	120	+	0	
12	LT2	F. 19	2	0	4	6	0	0	0	Saline and garlic
13	LV[1]	F. 10	3	0	2	17	7	0	0	
14	LV[1]	F. 6	3	0	1	4	4	+	0	
16	LV[1-II]	F. 81	5	60	3	60 s.a.	60	+	0	
23	LV[1]	F. 59	3	14	3	12	0	0	0	
24	RV[1]	F. 75	2	44+ (died)	9	41	44+ (died)	+	0	
		Mean 52·8 Median 61·5	Mean 3·8	Median 30	Median 3·5	Median 17	Median 52	5/10	1/10	

s.a. indicates secondary infection with *Staph. aureus*. These figures have been excluded from the calculations.

beneficial effect on zoster, it was apparent that some patients derived no benefit from the treatment. The intermittent application of the active substance would, of necessity, leave long gaps when virus presumably could multiply unhindered. Experience of treatment of herpetic whitlows (Juel-Jensen, 1970a) had shown that 40% idoxuridine in dimethyl sulphoxide was more effective than 5%, and that continuous treatment was more effective than intermittent. It seemed desirable to see if this was also the case in chicken-pox when the patient could act as his own control.

Two patients with chicken-pox were seen when the rash was only 24 hours old. With their consent an experiment was carried out in which a rectangle 20 by 10 cm. was marked on both sides of the front of the trunk, where there were ample lesions. To one area 5% idoxuridine in dimethyl sulphoxide was applied four times a day for four days, the opposite area was left untreated. In both patients application made no difference; new lesions appeared as on the other side, and the old lesions were not obviously behaving differently from those on the control side. It seemed reasonable to assume that as the skin was only intermittently wetted with the active substance new virus had ample opportunity of establishing infection in the skin and replicating during the intervals.

The work of Kligman (1965) showed that dimethyl sulph-

oxide is an admirable carrier of material dissolved in it. To make certain that an adequate concentration reached the affected cells it was decided to try the effect of 40% idoxuridine. British Drug Houses had produced an extra-pure form of dimethyl sulphoxide for spectroscopy. This was used as a solvent. The experiment on the lesions in the primary disease, chicken-pox, was repeated in two volunteers. Two areas, 20 by 10 cm. were marked on the right and left sides of the front of the trunk of the patient with a rash of 24 hours' duration. On one side a piece of lint 20 by 10 cm. was soaked in 40% idoxuridine in purified dimethyl sulphoxide and applied constantly with a bandage so that the active substance was in continuous contact with the skin. The rectangle on the other side acted as control.

At the end of 24 hours the lint was removed in the first patient. The already developed lesions had gone flat, and no new lesions had appeared. After the lint was removed, however, new lesions appeared which were staggered in their development by 24 hours compared with the other side. In the second patient the lint was kept applied for four days continuously, and rewetted daily. It was still damp at the end of 24 hours. The original lesions of the area disappeared, and at no stage did any new ones appear. The eruption in the untreated area followed its expected course. The amount of fluid needed to wet the lint on the first occasion was about 5 ml., and 2-3 ml. was used on each successive occasion, corresponding to a total of about 6 g. of idoxuridine in all, of which it is estimated that about half remained behind in the lint (which was reused to save the drug) by the increase in weight of the lint before and after use when the purified dimethyl sulphoxide had been allowed to evaporate. This would correspond to a maximum dose of about 750 mg., probably nearer 500 mg. a day or 10-15 mg./kg. body weight, which is much below the amounts used intravenously in the treatment of herpetic

TABLE III.—*Results of Uncontrolled Treatment of Zoster with 40% Idoxuridine in Purified Dimethyl Sulphoxide Continuously Applied*

Case No.	Site (Cranial or Segmental Nerve Concerned)	Sex and Age	Age of Lesion	Duration of Pain	Vesicles Dry	Scab Gone	Altered Sensation	Virus Cultures	Outlying Pocks
			Days From Start of Treatment						
1	RC3	M. 47	3	1	4	14	40	0	+
2	LV[1]	M. 60	1	3	3	7	0	+	
3	RT5	F. 55	3	3	1	11	0	0	
4	RC2	M. 21	2	2	3	11	0	0	+
5	RV[1]	F. 61	3	3	4	11	0	0	+
6	LV[1], LV[11]	F. 78	4	3	1	30	0	0	
7	LV[1]	M. 51	1	1	3	14	0	+	
8	RV[1]	F. 58	1	1	1	16	0	+	
9	LV[1]	M. 68	4	0	1	4	0	0	
10	LC7	F. 18	4	0	1	2	0	0	
11	LL5	F. 68	7	1	1	6	0	0	
12	RC2-3	F. 58	2	3	3	10	3	+	
13	LT5	F. 68	5	4	7	24 s.a.	0	+	
14	LV[1]	F. 58	2	1	2	3	23	0	
15	RC4	F. 70	2	1	1	4	0	0	
16	LV[1]	M. 26	7	9	6	9	0	0	
17	LC5	F. 29	3	7	5	20	0	+	+
18	RV[1]	M. 29	9	1	1	6	0	0	
19	RC6–7, T1	M. 19	7	1	2	14	0	0	
20	LT2	M. 52	3	2	5	18	0	+	
21	RV[1]	M. 62	2	1	1	3	0	0	
22	LV[1]	F. 82	6	3	4	10 + (died)	0	0	
		Mean 51·7 Median 58	Mean 3·7	Median 2	Median 2·5	Median 10	Median 32	7/22	5/22

TABLE IV.—*Results of a Double-blind Trial of Saline with Garlic, Purified Dimethyl Sulphoxide, and 40% Idoxuridine in Purified Dimethyl Sulphoxide Continuously Applied in Treatment of Zoster*

Case No.	Site (Cranial or Segmental Nerve Concerned)	Sex and Age	Age of Lesion	Duration of Pain	Dry Vesicles	Scab Gone	Altered Sensation	Virus Isolation	Outlying Pocks	
			Days from Start of Treatment							
2	RC4	F. 71	2	1	7	14	0	+	+	
4	LL2	F. 52	2	1	7	14	0	+	0	
6	LV[1+]	M. 51	1	3	1	8	8	+	0	
7	RT6	F. 26	4	3	1	7	6	+	0	
10	LT12	M. 64	1	1	1	8	0	0	0	40% idoxuridine in 100% Purified Dimethyl Sulphoxide
10a	LT11	M. 64	1	4	8	16	0	+	0	
13	LV[1]	M. 52	3	2	2	15	18	0	0	
14	LV[1]	M. 44	2	5	5	13	15	+	0	
16	LV[1+]	M. 63	3	3	4	22	40	+	0	
18	LV[1]	M. 54	3	1	1	14	38	+	0	
		Mean 54·1 Median 53	Mean 2·2	Median 3	Median 3	Median 14	Median 16·5	8/10	1/10	Patients with absent pain or absent altered sensation not included in these figures
3	LV[1]	F. 62	3	30	5	10	30	0	0	
5	LT3	M. 61	4	140	5	12	30	0	0	
8	RV[1+]	F. 63	3	36	10	34	50	+	0	
12	RT6	M. 61	3	20	17	24	0	+	0	100% Purified Dimethyl Sulphoxide
15	RV[1+]	F. 68	3	75	5	9	75	0	0	
19	RV[1+]	F. 86	5	78	5	65	50	+	0	
20	RT5	F. 63	3	65	6	20	0	+	0	
		Mean 66·2 Median 63	Mean 3·4	Median 65	Median 5	Median 20	Median 50	4/7	0/7	
1	RV[1+]	F. 65	3	115	13	40	103	+	+	
9	LL2	F. 55	4	4	2	10	11	0	0	Saline and garlic
11	LL3	M. 43	2	17	14	18	17	0	0	
17	RC3	F. 57	3	12	3	12	0	0	0	
		Mean 55·0 Median 58	Mean 3·0	Median 14·5	Median 8	Median 15	Median 17	1/4	1/4	

encephalitis. The patient's skin in no way suffered from the constant application. He was aware of a slight burning initially and the skin became slightly red.

Following this encouraging experiment the same method of treatment—that is, constant application of 40% idoxuridine on lint which was rewetted daily and kept in place by gauze and a bandage—was tried on a series of 22 patients with zoster of recent onset (Table III). Clinically it soon became apparent that the method was feasible. The lint soaked in the active substance remained moist and could be kept in place. The patients were delighted, for the pain disappeared within a median of two days. Healing also appeared to be accelerated. By chance only one of the patients (case 6) with ophthalmic zoster had involvement of the nasociliary branch. In none of the others did that branch become involved (care was taken to include the area of skin usually supplied by it), whereas this happened with intermittent treatment. The solution was well tolerated by all. There was slight peeling of the skin after the end of treatment, but in only one instance (Case 13) did secondary bacterial infection occur. Regular blood counts on all patients did not reveal any abnormalities of haemoglobin, white blood cells, or platelets, nor was there any evidence of disturbance of liver function as monitored by S.G.P.T. estimations. This form of treatment was subjected to a double-blind trial carried out from April to September 1969.

Results

The results are set out in Table IV. Twenty patients participated (of these one had a fresh attack in a different segment and was entered again, making 21 patient attacks). The average age of the lesions before the patients were first seen was of the same order (2·2, 3·4, and 3·0 days) in the three groups.

All the patients had pain. There was no statistically significant effect of age or sex on the duration of pain, but as in the former trial, more patients of 60 or above had pain of long duration; but only in the control groups (six in the purified dimethyl sulphoxide group, one in the saline group) did pain last for more than 20 days, whereas the longest period of pain in those aged 59 or below (saline group) was 17 days.

The group treated with idoxuridine did much better than the two control groups. The pain had gone after a median of three days, as compared with a median of 65 days for the purified dimethyl sulphoxide and 14·5 days for the saline and garlic groups. There appears to be a positive disadvantage in the continuous treatment with purified dimethyl sulphoxide as compared with saline alone, but the numbers are small.

It was striking that no new lesions appeared in any patient treated with continuous idoxuridine in this trial or in the uncontrolled series once treatment had started in the area affected so long as it was covered with the wet lint, whereas this often happened in the placebo groups. In none of the patients with ophthalmic zoster was the nasociliary branch involved once treatment had started.

Virus cultures were positive in 13 of the 20 patients. In the rest a high or rising titre of antibody confirmed the diagnosis. As before, haematological and biochemical tests showed no abnormality apart from a transient appearance of atypical mononuclear cells in one or two patients.

The results from the two double-blind controlled trials and the two uncontrolled series were tested statistically. There was no statistically significant difference between the uncontrolled and controlled groups of patients treated with 5% intermittent idoxuridine in dimethyl sulphoxide, and between the uncontrolled and controlled groups treated with 40% continuous idoxuridine in purified dimethyl sulphoxide, so all the patients treated with 5% idoxuridine were merged into one group and all those treated with 40% idoxuridine into another. For the same reason all patients treated with placebo (whether intermittent or continuous saline and garlic) were merged. The figures were subjected to rank testing (Mantel, 1967), the results are summarized in Table V.

From these calculations it is clear that there is an undoubted benefit from the treatment with continuous 40% idoxuridine in purified dimethyl sulphoxide on the duration of pain. This, in spite of modest numbers, is true of the results from the double-blind controlled trial alone, and when uncontrolled and controlled results are pooled the results are highly significant ($P<0.00001$).

In the double-blind trial the difference between the time to healing in the two groups was not statistically significant, but in the larger group the time the vesicles took to dry (2·5 against 3·5 days) was significantly shorter, and complete healing occurred after 11 days in the actively treated group, as against 17 days in the placebo groups, a difference which was statistically significant. In both instances there was a shortening of about 30% of the time to healing.

When all patients with 5% intermittent idoxuridine are compared with all treated with true placebo, only the duration of pain is significantly shortened by the active treatment (5 days against 17 days). There is no significant shortening of the time to healing.

Though the figures suggested that continuously applied purified dimethyl sulphoxide by itself might have a deleterious effect, the difference is not statistically significant. Finally, when all patients treated with 40% idoxuridine in purified dimethyl sulphoxide are compared with all treated with 5% idoxuridine in dimethyl sulphoxide, the superiority of the former (median 2·5 against 5 days) is statistically highly significant ($P=0.0003$).

Discussion

These trials show that there is a very definite place for idoxuridine in the treatment of zoster, as might have been expected on theoretical grounds. The way the material is applied appears to be crucial. It could reasonably be argued that it is possible that a lower concentration of idoxuridine might suffice for continuous application. Idoxuridine is potentially mutagenic, and though the amount absorbed by the patient, even when extensive segments have been covered, probably at the most would approach 20–25 mg./kg./day, one would like to keep the amount as low as possible. Uncontrolled trials of 5% and 20% solutions suggest that the effect is inferior to the 40% solution, but a controlled trial to

TABLE V.—*Statistical Significance of the Results Obtained in Trials of Idoxuridine in Dimethyl Sulphoxide (DMSO) and in Purified Dimethyl Sulphoxide (DMSO-S) in the Treatment of Zoster*

	Controlled Trial. Continuously Applied 40% Idoxuridine in DMSO-S *Versus* Continuous Saline and Garlic		Uncontrolled and Controlled 40% Idoxuridine in DMSO-S *Versus* All Saline and Garlic		Controlled and Uncontrolled 5% Idoxuridine in DMSO *Versus* All Saline and Garlic		Continuously Applied DMSO-S *Versus* Saline and Garlic		All 40% Idoxuridine in DMSO Continuously Applied *Versus* 5% Idoxuridine Intermittently Applied	
	Days*	P	Days*	P	Days*	P	Days*	P	Days*	P
Pain	3:14·5	0·01	2·5:17	<0·00001	5:17	0·015	65:17	N.S.	2·5:5	0·0003
Vesicles dry	3: 8	N.S.	2·5: 3·5	0·02	4: 3·5	N.S.	6: 3·5	N.S.		
Scab gone	14:13	N.S.	11 :17	0·04	20:17	N.S.	20:17	N.S.		

*The duration given is the median in days for the two contrasted groups. Not significant taken as $P>0.05$.

resolve this is in progress. Elliott (1964) reported that high doses of prednisolone given to patients with zoster of recent onset and severe pain led to a reduction of the duration of pain to an average of 3·5 days from an average of 3·5 weeks in untreated patients. Eaglstein *et al.* (1970) reported a similar effect from triamcinolone, though two elderly patients did not benefit. Though those writers did not report adverse effects, the potential hazard of the use of steroids in zoster—namely dissemination of the virus—has been emphasized by Merselis *et al.* (1964).

In very extensive zoster, such as generalized zoster in patients on immunosuppressive drugs and/or steroids, the local application may not be feasible, though Calabresi (1965) tried the use of systemic idoxuridine in very large doses, with equivocal results. In such patients the use of cytosine arabinoside, another antiviral drug, should be considered (Juel-Jensen, 1970b; Hall *et al.*, 1970). At present, for the ordinary case of zoster the treatment outlined above appears to be of great benefit to the patients, and offers a real advantage in shortening the duration of that most dreaded of all consequences of zoster—pain.

Our thanks are due to Miss Ivy Poole, without whose devoted nursing expertise these trials would not have been possible; to Mr. Ivor Chinn for his help with virus cultures; to Dr. A. H. Tomlinson for assay of varicella-zoster antibodies; to Dr. Alan Sharp and his colleagues for haematological investigations; to Dr. M. M. Pickles for immunoglobulin assays; to Mr. J. R. P. O'Brien for biochemical investigations; and to Miss M. G. Craig, chief pharmacist, Radcliffe Infirmary, for her help.

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Cyanide Self-poisoning

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Summary: Four cases of cyanide self-poisoning were admitted to one hospital over a period of two years. Two of the patients died. The diagnosis in the unconscious patient may be suggested by the finding of bradycardia and the absence of cyanosis (despite inadequate ventilation). The diagnosis can be confirmed in 5 to 10 minutes by a simple test on gastric aspirate, performed by the casualty officer. Cardiac pacing was used in two patients and may have a place in the supportive management of severe cases.

Introduction

The diagnosis of cyanide poisoning is a matter of the utmost urgency if a lethal outcome is to be avoided. There are certain clinical features which may immediately suggest the diagnosis, but a simple and rapid confirmatory test would be most valuable.

The widespread industrial use of cyanides makes these compounds readily available for deliberate acts of self-poisoning, and sporadic cases are to be expected. Four such cases have been seen at this hospital in the past two years. This paper describes these briefly to illustrate some points of importance in the clinical diagnosis, and to suggest a simple biochemical examination which may be performed on gastric aspirate when confirmation of the diagnosis is required.

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Case Reports

Case 1.—A 25-year-old man arrived at the accident and emergency department at midnight, deeply unconscious. He was pulseless and apnoeic, but the skin was warm and the mucous membranes were pink. He was in cardiac asystole and, because cardiac action was not restored by external cardiac massage and intravenous isoprenaline, a transvenous bipolar pacemaker catheter was introduced into the right ventricle. Cardiac response to the pacemaker impulse was intermittent and he died 30 minutes after admission. Forensic examination showed cyanide in blood and tissues.

Case 2.—A 35-year-old man was found unconscious in the street at midday. On admission he was deeply unconscious, with fixed dilated pupils and absent deep tendon reflexes. The blood pressure was unrecordable, the heart rate 40 per minute. Though he was not cyanosed, respirations were shallow and infrequent. Ventilation was assisted manually via a cuffed endotracheal tube, and in view of the possibility of subarachnoid haemorrhage lumbar puncture was performed. Clear cerebrospinal fluid was obtained under normal pressure. Within minutes of completing this procedure cardiac asystole occurred; external cardiac massage restored a sinus bradycardia of 28 per minute. Intravenous isoprenaline achieved a heart rate of 70-80 per minute with a palpable radial pulse, but the chronotropic effect was transient. A transvenous pacemaker catheter was therefore introduced into the right ventricle and pacing begun. At this time a document was found in his clothing which was in the nature of a "suicide note," whereupon a presumptive diagnosis of cyanide poisoning was made. Treatment with 10 ml. of 3% sodium nitrite and 25 ml. of 50% sodium thiosulphate intravenously was started, but asystole recurred and the ventricle failed to respond to the pacemaker impulse. Forensic examination confirmed the presence of cyanide in the stomach and blood. It was subsequently discovered that the patient obtained the cyanide at his place of work, a local chemical factory.

Case 3.—A 25-year-old bacteriology technician took about 1 g.