EUMYDRINE IN PYLORIC STENOSIS

BY

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The treatment of pyloric stenosis by eumydrine was introduced by Svensgaard in 1935. Sixty-one cases were treated, with controls. The immediate results were diminished period of vomiting, shortened stay in hospital and better increment in weight. Braithwaite (1937) gave a brief report of twenty-two cases, of which eighteen were successful and four relieved by surgery. This paper gives an account of eumydrine, of experience of the drug at welfare centres and of results of its use in Guy's Hospital. When it was virtually completed an article on the treatment of pyloric stenosis by eumydrine by Dobbs (1939) appeared, to which reference is made later.

Physiology

In pyloric stenosis of infancy there is an interference with the normal opening of the pylorus ; food leaves the stomach with difficulty and some of it is vomited ; the pylorus is hypertrophied and may be palpable ; gastric peristalsis is visible. Atropine is known to be beneficial in relieving the spasm of the sphincter ; eumydrine, chemically related to atropine, is much more successful, but the mode of action of neither drug is quite clear.

The opening of the pylorus has been studied by McSwiney and Pyrah (1932) in dogs. The sphincter is normally closed. When a wave of contraction starts in the pyloric antrum the sphincter relaxes and remains open for five to six seconds. About a second before the wave reaches its summit the sphincter closes again and stays closed during the remainder of this wave and afterwards until the next. These movements are governed by the intrinsic nervous system. The opening and closing can be influenced by local events. Serdjukow (Pawlow, 1902) produced closure of the pylorus by introducing acid into the duodenum and relaxation by increasing acidity in the stomach. This action is independent of the central nervous system. In time clinicians became aware that acidity of contents is not of great importance, because persons with achlorhydria may yet have a normal emptying time. McSwiney and Spurrell (1933) found the osmotic pressure of the gastric contents was more important. Hypertonic meals cause delay in emptying, and hypotonic leave more quickly than isotonic. Spurrell (1935) found that alterations in the pressure of the duodenal contents affected the rate of emptying. Using cats he observed that with a duodenal pressure of 10 cm. of water, 60 c.c. of saline were evacuated in five to ten minutes, but when the pressure was raised to 30 cm. the rate of outflow was halved. He attributed this reflex to the splanchnic nerves, since in his preparation the intrinsic nerves are divided. Section of the vagi had no effect.

The stomach with its double nerve supply, vagal and sympathetic, can be influenced by other viscera, by the central nervous system, and even by the

brain, since the sympathetic depends on nuclei in the hypothalamus. The actions of the vagi and sympathetic have been reviewed by McSwiney (1931). Section of vagi causes diminished tone, slow peristalsis and delayed emptying. Stimulation usually causes dilatation of the pyloric sphincter and increase in tone and movement of the stomach ; but if the stomach is already in a state of high tonus the result is the opposite. The vagus, in short, is predominantly motor to the stomach and dilator to the sphincter ; but the effect is not pure. Stimulation of the splanchnic nerves causes the body to relax and the sphincter usually to contract ; but if the sphincter is already hypertonic it relaxes. What happens when either of these nerves is stimulated depends not only on which nerve it is but also on the state of the stomach. One nerve under the right conditions will do what the other does under other conditions. These mixed effects are not due to mixture of fibres, according to Spurrell, but to overlapping of functions. When consideration is given as to which nerve might be responsible for a spasmodic closure of the sphincter in pyloric stenosis and be paralysed when the spasm is relieved by atropine or eumydrine, there are difficulties. It seems that the end-organs that cause closure of the pylorus can be excited by a great variety of stimuli and can be influenced by both the sympathetic and the vagus, and by the intrinsic nerves, but predominantly by the sympathetic. Supposing that there are such influences descending to one or other of these nerves, whence do they come ? There seems no answer yet to this question except the rather far-fetched idea that pyloric stenosis is a disease of the same order as asthma, dependent in part on the personality of the patient. That these patients often have a particular kind of personality, masculine, vigorous and alert, is generally recognized. But is there a genuine spasm of the pyloric sphincter at all ? Doubt has even been thrown on this.

Achalasia.—This is a condition in which the cardiac sphincter fails to open, coming on later in life and said to be due to degeneration of Auerbach's plexus (Hurst, 1924). It might be supposed by analogy that pyloric stenosis was a condition in which the pyloric sphincter failed to open in infancy owing to delayed development of the appropriate nerve fibres. But there is one striking difference that seems to preclude the idea ; the cardiac sphincter is never hypertrophied, whereas the pyloric sphincter is prominently so. The one is merely not relaxed, the other actively and abnormally constricted—or so it seems ; but according to Cameron (1926) it is not the sphincter that is hypertrophied at all, but something else, namely the pyloric canal. This he describes as part of the expelling apparatus of the stomach, not of the retaining : a long, cylindrical tube of circular muscular fibre, thickened from abnormal effort to push the stomach contents past a passively closed sphincter (Cameron, 1926). This view, he says, is in keeping with clinical and radiographical evidence. It seems also to fit in well with the naked-eye appearance of the stomach. It has the merit of simplicity and it makes the actions of atropine and eumydrine fairly comprehensible, though not more so than the spasmodic view.

Pharmacology

Atropine has a general paralytic effect on nerve endings in the stomach. McCrae and Macdonald (1928) studied the effect of atropine given intravenously to cats. There was a general relaxation of the stomach, with fall in intra-gastric pressure, arrest of all movements for at least four hours and absence of response to stimulation of any nerve. No mention was made of special effect on the pyloric sphincter. Previous observers (cited by them) obtained results that were in all important respects the same. The dose of atropine given to a child is smaller than that used in these experiments (0.05 mgm. against 0.1 to 0.15 mgm.) and it is given by mouth. The effects therefore may not be quite

the same. Visible peristalsis, for instance, is not abolished, but goes on at least for a time. If pyloric stenosis is a spasm of the sphincter, then medicinal doses of atropine which are beneficial must be blocking impulses to the sphincter without inhibiting peristalsis. But if it be an achalasia, then the general relaxation described, in which the sphincter presumably shares, is reached before peristalsis is abolished. The action of atropine as at present known throws little light on the cause of the disease ; but there is this to be considered : both atropine and eumydrine sometimes fail in their effect, even if the dose is increased. Is not the likely explanation of this that constrictor impulses are reaching the sphincter too powerful for the drug in medicinal dose to abolish ?

EUMYDRINE.—Atropine (1) is an ester formed from the base tropine and the acid tropic acid, with elimination of water. Tropine is both a tertiary base (amine) and a secondary alcohol. Its peculiar feature is the nitrogen bridge with methyl group attached. Tropic acid is phenyl hydracrylic acid. Tropine itself has no pharmacological action.

Numbers of substances have been tried in which other acids have been combined with atropine, of which the best known is homatropine, the compound with mandelic acid. Of the rest some are toxic and some inactive. Alteration in the attachments to the nitrogen bridge gives another variety of compounds. Demethylation, for instance, produces diminished activity. Noratropine, the substance formed, has one-eighth of the activity of atropine (Dyson, 1928). The reverse change can also be produced in the following way. Atropine can, like ammonia, add itself to acids ; in fact, it is usually administered as a sulphate on account of its much greater solubility. The nitrogen atom has now become quinquivalent instead of trivalent. One of the extra valencies takes up the acid and the other the hydrogen atom. This hydrogen atom can be substituted by a methyl group, so that there are now two attached to the nitrogen bridge : if the acid in combination at the same time is nitric acid, the result is eumydrine or atropine methyl nitrate (2).

Eumydrine was intended as a mydriatic. It is sometimes used when atropine irritates the eye ; but in this country it has not been well known. Svensgaard in her paper stated that it was one-fiftieth as toxic as atropine, but gave no particulars nor reference. Dyson is exiguous, but illuminating. He says that as a result of the chemical change from atropine to the dimethyl quaternary ammonium salt the action is diverted from the remainder of the nervous system to the peripheral nerve-endings (Dyson, 1928). This goes far to explain the superiority of eumydrine over atropine. It means that a larger dose can be given with a greater local effect and less danger of poisoning. In actual fact I have not seen eumydrine produce any effects at all except

locally ; there is neither mydriasis, rapid pulse, flushing, dry mouth, nor any other sign when it is given by mouth. It is unstable on solution ; perhaps it is quickly destroyed on absorption.

Experience of eumydrine

The patients for whom eumydrine was used were seen at welfare centres, which means that they should have been, and actually were, caught early and treated promptly. Most were treated in the observation wards of the Borough of Poplar, where good nursing greatly helped towards success. I was also fortunate in having six mothers out of seven of exceptional merit, and a seventh who was at least of average goodness. Furthermore six out of the seven babies were breast-fed. In these circumstances the drug acted excellently. In not less than forty-eight hours vomiting had begun to diminish, the weight ceased to fall, pain grew less and sleep and contentment took its place. The visit to the first child two days after admission showed dramatic improvement which was steadily maintained. No relapses occurred in any of the seven cases ; there were no signs of toxicity and no after-effects of the illness. Reviewed at four months, the patients appeared a perfectly normal set of children (except for the undernourished condition of the child of the least satisfactory mother, who was beginning bottle feeding). The time spent in the wards was curtailed as experience was gained, and in the end two children were actually treated as out-patients with success. It is not contended, however, that severe cases might not still require operation, especially if they escaped observation until too late.

The dose of the drug was the same as that used by Svensgaard, namely 0.25 mgm. given half an hour before each feed, dissolved in one drachm of water ; but five feeds a day and not seven were given. Fresh solutions were made up weekly. The criteria of the disease were projectile vomiting, visible gastric peristalsis, constipation and loss of weight. Distinction between pyloric stenosis and pyloric spasm appears meaningless nowadays.

Case reports

R.B. showed characteristic rise of weight at the beginning of her life, followed by a fall when symptoms began in the fifth week. After two days of vomiting the baby was brought to the welfare centre and gastric peristalsis was easily visible, accompanied by obvious discomfort. The baby was admitted at once. Vomiting was projectile and occurred at least once after every feed. The bowels were not opened for five days. Eumydrine was begun at once. For twenty-four hours there was little change in the child and a further slight fall in weight. But in forty-eight hours vomiting had much diminished, weight had begun to rise and the whole aspect of the child had altered for the better. On the fourth day the weight lost was regained, on the sixth vomiting ceased altogether, and on the tenth peristalsis was last observed. She was discharged on the nineteenth day. Treatment was stopped in six weeks. This child was the only female and she was breast-fed.

F.W.—Vomiting began in the fourth week, seven days before admission. There was a loss in weight of 18 oz. There was much pain after food, copious vomiting and vigorous peristalsis. Improvement began with arrest in the fall

of weight on the third day after treatment. On the fourth there was a sharp rise with dramatic remission of symptoms. The last vomit occurred on the eleventh day and the patient was discharged on the thirteenth. The previous weight was regained on the twentieth day. Peristalsis was visible for five weeks. The drug was withdrawn at the ninth week, but vomiting started again and it was administered until the thirteenth week. This was a vigorous breast-fed baby with an exceptionally good mother, who recognized the nature of the disease, having seen it in a nephew.

R.S.—Vomiting began in the fourth week. The mother was prompt and brought her baby for admission after two days. The amount of weight lost was doubtful, as he had not been weighed for a fortnight. The weight at birth was 6 lb., and in the fourth week 5 lb. 15 oz. The usual symptoms were present and the peristalsis was obviously painful. This early case was promptly relieved. Projectile vomiting actually stopped in twenty-four hours and all vomiting in seven days. He was discharged after twelve days. Eumydrine was administered for thirteen weeks. He was a slightly small but otherwise normal breast-fed baby.

B.B. had been sick since birth, but between the third and fourth weeks the vomiting became worse. He lost twelve ounces and passed no faeces for eight days. Peristalsis of considerable intensity with pain was easily seen. Vomiting was projectile. Improvement was rapid. In forty-eight hours there was a substantial gain in weight. Vomiting became less forcible and frequent. After seven days it stopped altogether. He was discharged on the seventh day; weight was regained by the twelfth day. Eumydrine was administered for eleven weeks. Peristalsis was active for some time, but disappeared after eight weeks. He was a lusty breast-fed baby.

A.B. was the only bottle-fed baby. For five weeks after birth he did well. He began to vomit in the sixth week and had lost 10 oz. in weight by the eighth. There were forcible vomiting, visible peristalsis with crying and constipation. After eumydrine was given vomiting stopped in three days. The baby was discharged in seven days and regained his weight in ten days. Eumydrine was given for sixteen weeks. He was fed on a preparation of lactic acid milk. He became perfectly healthy and normal.

TABLE 1

	HISTORY, LENGTH (DAYS)	WEIGHT LOST (OUNCES)	DAYS TAKEN TO REGAIN WEIGHT	DAYS TAKEN TO CEASE VOMITING	DAYS IN HOSPITAL	EUMYDRINE ADMINISTRATION (WEEKS)	WEIGHT AT 4 MONTHS MORE OR LESS THAN AVERAGE (OUNCES)
R.B.	3	6	4	6	19	6	+ 8
F.W.	7	18	20	11	13	13	+34
R.S.	2	not known	—	7	12	13	— 5
B.B.	indefinite	12	12	10	7	11	+22
A.B.	21	10	10	3	7	16	—20
L.D.	4	1	4	4	—	13	+16
H.K.	5	not known	—	5	—	9	—40
Aver- age Svens- gaard	7	8	10 7	7 21	8 69	11	+ 2

L.D.—No symptoms occurred until the third week. The baby was sick for three days ; on the fourth day he was seen and found to have projectile vomiting, and visible peristalsis with squirming movements. He had lost 1 oz. He was in such good condition that it was decided to try out-patient treatment at the Royal College of St. Katharine, Poplar. He vomited for four days after treatment, at first copiously, then only once or twice a day. After that he did not vomit again. Peristalsis was visible for five weeks, eumydrine being given for thirteen weeks.

H.K.—His mother reported that his vomit was sufficiently forcible to shoot across a railway carriage. He was seven weeks old when seen, and the history dated back five days. He weighed only 7 lb. 12 oz., but as he had not been weighed since birth it was impossible to say how much he had lost. Peristalsis and constipation were noted. He was not desperately ill and as his mother was an intelligent woman of the professional class it was decided to try treatment at home. Vomiting stopped five days after treatment and there was a gain of 3 oz. in the first week. The child was much quieter and happier. Eumydrine was continued for nine weeks and there was no relapse. But she did not do very well with him and lost her breast-milk.

Results in Guy's Hospital

It was Dr. H. C. Cameron's successful use of the drug in Guy's Hospital that first prompted me to try it. He had kindly allowed me to examine the results of his treatment there (eleven cases). There are also three who were under the care of Dr. Ellis, which I have his kind permission to include, making a total of fourteen. Scrutiny of the reports shows that the criteria of what constitutes pyloric stenosis were the same as those I adopted. The methods of treatment and dosage (0.25 mgm.) were exactly the same, except that in two instances for a short time the dose was increased to 0.5 mgm. There is one difference, namely in the time that elapsed between onset and treatment. On an average it is more than two-and-a-half times as long in the hospital cases as in the welfare cases. The reason for this is quite obvious. Naturally the patients were also longer in hospital, more than twice as long. Supporting treatment was needed in four cases, that is saline infusions and blood transfusions. There is one death to record, from bronchopneumonia. It would be unjust to blame either the treatment or the disease itself, since all vomiting had stopped for a week, weight had increased by three hundred grammes and the patient's progress was satisfactory when the infection occurred. He was one of those, in fact, who came into hospital with one disease and died of another. Minor points to mention were that two were females and a surprisingly small number were breast-fed, only three children wholly and two partially. The favourite substitute was lactic acid milk.

In spite of the disadvantages of a comparatively late start and of much bottle-feeding, the treatment was highly successful. There are no failures to record. Vomiting was controlled in the same average number of days (seven) as in my own easier series. The longest time was thirty-six days and the shortest one day. It is unfortunately not possible to compare the regaining of weight. Nothing is known of the weight of these children at the time when symptoms began. It is only possible to record how long they took to regain

their weight on admission ; this was seven days. No signs of toxicity were recorded. Complications or, better, intercurrent infections occurred twice ; an otorrhoea and the aforesaid bronchopneumonia.

Judged by these twenty-one cases in all, administration of eumydrine is a rapid, harmless and successful method of relieving the pyloric stenosis of infancy. Its introduction, apparently by Svensgaard, has been a genuine advance in medical treatment.

TABLE 2
GUY'S HOSPITAL SERIES

Number	14	Vomiting abolished, days (average)	7
Days in hospital (average)	18	Death (bronchopneumonia) ..	1
History of vomit, days, (average) ..	19	Surgery	nil

Before concluding some reference may be made to the recent paper by Dobbs (1939) describing twenty cases in University College Hospital and elsewhere. My paper was written independently of his ; but the description of the successful use of the drug, the results obtained and the conclusions drawn are corroborative. On the whole the results at University College Hospital were a little less favourable than those we reported, since surgical intervention was resorted to in three cases and there was one death, not from intercurrent infection but from paralytic ileus, which was attributed to the eumydrine itself. Somewhat larger doses were usual (0.3 mgm.) ; and treatment was delayed from twelve to eighteen hours after admission. The general practice at Guy's Hospital was to begin at once. Dobbs also resorted to saline infusions as a routine, which was not found necessary in the present series except as stated.

Conclusions

1. Eumydrine causes relaxation of the gastric musculature. It has a pronounced local and an insignificant general effect.
2. It relaxes the pylorus in pyloric stenosis of infancy.
3. It is a safe, rapid and successful remedy for this condition.
4. Success is uniform in the present series, but may not always be so.
5. Vomiting is abolished in most cases within seven days.
6. Weight is regained in most cases within eight days.
7. Stay in hospital can generally be short ; mild cases can be treated as out-patients.

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