Continuous infusion of frusemide in refractory oedema

Frusemide is a potent loop diuretic with an impressive dose-response relationship over a wide dose range. Nevertheless, probably because of concern over possible toxicity,¹ the attainment of an effective dose may be delayed in patients with oedema refractory to conventional dosing. We report here the frequency with which high-dose frusemide was prescribed in a group of medical inpatients and then describe a small series of patients who were given continuous infusion of frusemide using a constant infusion pump.

Patients, methods, and results

During 1973 a study of prescribing habits was carried out in the medical division of Glasgow Royal Infirmary.² Details of drug use were recorded in 5288 consecutive admissions. A total of 1292 (24%) patients received frusemide, the mean daily dose received being up to 40 mg in 58% of recipients, 41-240 mg in 30%, and over 240 mg in 12%. Patients receiving up to 40 mg daily stayed on average 13 (SD 8) days in hospital compared with 16 (SD 9) days for those receiving over 240 mg daily. One factor that partially explained the increase in length of stay in the high-dose group was the time taken to attain an effective dose of frusemide. In view of this 10 patients (five men, five women) suffering from congestive cardiac failure who had failed to respond with a diuresis to 120 mg frusemide orally were given a constant infusion of frusemide intravenously. The average age of the patients was 67.5 years (range 60-75 years).

All patients attained satisfactory diuresis, but there was no correlation between the urinary output or urinary potassium or sodium concentration and the rate of frusemide infusion (table). The average urine volume during infusion ($\pm$ SE of mean) was 3.5 ± 0.8 ml/min, average urinary sodium concentration 80 ± 9.8 mmol(mEq)/l and urinary potassium concentration 21 ± 2.4 mmol(mEq)/l. Preinfusion data were available for five of the subjects and in all five there were substantial increases in peak minute urine volume (1 ml before, 5.1 ml after infusion), urinary sodium excretion rates (58 and 327 mmol/12 hours respectively), and potassium excretion rates (29 and 80 mmol/12 hours respectively).

The mean admission plasma potassium concentration was 3.8 ± 0.1 mmol/l and this fell to 3.5 ± 0.2 mmol/l after completion of the infusion. No patient received supplementary potassium treatment during the study and four developed hypokalaemia (plasma $K^+ < 3.5$ mmol/l); the lowest plasma potassium concentrations were 3.0, 3.1, 3.2, and 3.4 mmol/l.

No patient developed hyponatraemia, glycosuria, gout, or impaired hearing during the infusion. The mean plasma urate concentrations after the infusion were 412 ± 23 mmol/l (6924 ± 386 mg/100 ml).

Comment

Since an appreciable number of patients with cardiac failure need high-dose frusemide before a diuresis is obtained, with consequent prolongation of their stay in hospital, we assessed the feasibility and safety of administering frusemide in low doses by continuous infusion. All responded to this treatment, the only complication being mild hypokalaemia in those with the greatest urinary outputs, who were not receiving potassium supplements at the time. This method of administration avoids large bolus doses by mouth or by injection, permits a controlled gentle diuresis to occur, and thereby avoids the risk of prostatism in elderly men subject to intensive diuretic treatment. The rate of infusion required varied from 4-16 mg/h and could be increased stepwise until the desired effect was obtained. In the present study plasma frusemide concentrations of 0.5 mg/l were associated with peak sodium excretion rates of 5.5 mmol/min; this rate was equivalent to that found at plasma concentrations greater than 10 mg/l after an 80-mg intravenous dose.³ Thus effective diuresis was

achieved at blood concentrations considerably below those at which extrarenal effects of frusemide are seen.⁴

¹ Greenblatt, D J, *et al*, *American Heart Journal*, 1977, 94, 6.

² Kescon, C M, Gray, J M B, and Lawson, D H, *British Medical Journal*, 1976, 1, 680.

³ Branch, R A, *et al*, *British Journal of Clinical Pharmacology*, 1977, 4, 121.

⁴ Rupp, W, *Scottish Medical Journal*, 1974, 19, suppl p 5.

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Clinical Pharmacology Service, Glasgow Royal Infirmary, School of Pharmaceutical Science, University of Strathclyde, Glasgow

D H LAWSON, MD, FRCP, professor

J M B GRAY, MB, BCH, research registrar

D A HENRY, MRCP, registrar

W J TILSTONE, PHD, MRCPATH, lecturer

Cyanoacrylate adhesive for foreign body removal

We report the use of cyanoacrylate adhesive in removing an impacted oesophageal foreign body.

Case report

A severely mentally retarded 18-year-old man in an institution was referred to our unit with a one-week history of inability to take solid food. He had been admitted on three previous occasions after ingesting foreign bodies, laparotomy being required on one occasion. He was clinically dehydrated, but had no other abnormal physical signs. Plain radiography showed numerous radio-opaque foreign bodies in his gastrointestinal tract, including one in the upper oesophagus.

Oesophagoscopy under general anaesthesia showed a 4 cm $\times$ 3 cm $\times$ 3 cm stone at 20 cm, with a smooth, rounded surface presenting which could not be grasped by any instrument. A 14 FG Foley type catheter with a 25-ml balloon could be passed beyond the stone¹ using an introducer, but when traction was applied with the balloon inflated the stone merely rotated, allowing the balloon to pass alongside. The surface of the stone was carefully cleaned with methylated spirit. Cyanoacrylate adhesive (Superglue 3,

Foreign body attached to rigid plastic tube with cyanoacrylate adhesive, inflated Foley catheter, and pharyngoscope after removal from oesophagus.

Effect of frusemide infusions on urine volume and electrolyte excretion

Case No	Age and sex	Peak urine flow (ml/min)	Frusemide infusion rate (mg/h)	Frusemide plasma concentration (mg/l)	Urinary sodium (mmol/l)	Urinary potassium (mmol/l)	Urine volume per 24 h (l)
1	60 M	5.2	4	0.4	112	21	7.5
2	65 M	2.5	5	0.4	36	9	3.6
3	60 F	9.8	8	0.7	85	25	14.1
4	67 M	2.5	8	0.9	34	36	3.6
5	73 F	2.4	8	0.7	114	22	3.5
6	72 F	2.8	8		113	22	4.0
7	72 F	1.6	10	0.8	59	21	2.3
8	62 M	5.0	10	0.6	92	10	7.2
9	68 F	1.4	12	0.9	97	21	2.0
10	75 M	1.9	16		60	23	2.7

Loctite) was applied to the end of a rigid 5-mm OD plastic tube, which was then rapidly passed down the Roberts pharyngoscope and pressed firmly on to the stone, meanwhile applying countertraction with the inflated Foley catheter, which had been re-introduced. The stone was then extracted by withdrawing plastic rod, catheter, and pharyngoscope as one (see figure). The patient made a rapid uneventful recovery without oesophageal perforation.

Comment

Oesophageal foreign bodies should be removed as a matter of urgency²; cyanoacrylate adhesive, with its ability to form rapidly a strong bond even between moist surfaces,³ extends the range of endoscopic extraction techniques. High tensile strength can be achieved by this method, provided the presence of gross blood and mucus does not interfere, and a "peeling" action, which is effective in separating bonded tissues,⁴ is avoided.

In this case a large stone impacted in the oesophagus could not be removed using conventional techniques. Our method rendered removal possible without recourse to major surgery.

¹ Bonfils-Roberts, E A, *et al*, *Annals of Thoracic Surgery*, 1975, **19**, 196.

² *British Medical Journal*, 1975, **4**, 368.

³ De Fonseca, C P, *British Medical Journal*, 1976, **3**, 234.

⁴ O'Sullivan, D J, *British Medical Journal*, 1976, **2**, 109.

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Cardiothoracic Unit, Groby Road Hospital, Leicester

D S MACPHERSON, FRCS, surgical registrar
R WYATT, FFARCS, consultant anaesthetist

Interpretation of serum total thyroxine concentration in patients with abnormal thyroxine-binding proteins

The free thyroxine index (FTI), the ratio of serum total thyroxine concentration (T4) to the unsaturated thyroid hormone binding capacity (THBC), may be misleading in patients with abnormal concentrations of binding proteins,¹ although designed to compensate for such abnormalities.² In euthyroid patients with a wide range of THBC we found a "zero error" in THBC (Thyopac-3). We have solved this problem by a simple modification of FTI.

Patients, methods, and results

We have studied 200 clinically euthyroid patients with a wide range of THBC values comprising 59 pregnant women, 57 non-pregnant women, 19 patients with nephrotic syndrome, 27 with chronic liver disease, and 38 members of families with inherited abnormalities of thyroxine-binding globulin (TBG). Dr W A Burr and his colleagues in Birmingham kindly supplied the primary data for 34 of the patients in this last group. Serum T4 (nmol/l) was measured by Thyopac-4 (Amersham) except for the Birmingham patients, in whom it was measured by radioimmunoassay. THBC was measured as per cent of mean normal by Thyopac-3 (Amersham). The 200 euthyroid patients had conventional FTI values which fitted neither a Gaussian nor a logarithmic distribution and which ranged from 8 to 217 (normal 45-145).

The figure shows that, as T4 decreased, THBC approached values near 50% rather than zero. Thus calculation of the simple ratio (FTI) is inappropriate. The spread of THBC values made subtraction of a constant from THBC unsatisfactory. The simplest solution was to determine an optimum negative intercept on the T4 axis to calculate a modified FTI. This value was -80 nmol/l. The modified FTI values, calculated as $(T4 + 80) \times 100 / THBC$, fitted a logarithmic distribution closely. Independent data from 199 euthyroid adults and 123 euthyroid geriatric patients gave logarithmic means and standard deviations which did not differ from the values for our patients ($P > 0.3$). As expected, 5% of our 200 patients fell outside the modified FTI range (118-235), whereas 16% fell outside the conventional FTI range.

Measurements made on specimens from 2023 patients by Thyopac methods in six months were searched for discordant classification by the conventional and modified FTI. By definition 95% reference ranges produce

Relation between T4 and THBC in 200 euthyroid patients with a wide range of values for THBC. Dotted lines are 95% limits of conventional FTI and continuous lines 95% limits of modified FTI.

▲ = Inherited abnormalities of TBG. ○ = Nephrotic syndrome. ■ = Chronic liver disease. □ = Non-pregnant women. ● = Pregnant women.

Conversion: SI to traditional units—Serum thyroxine: 1 nmol/l $\approx$ 0.08 μ g/100 ml.

5% of "abnormal results" in healthy populations. We looked for patients who fell within the 95% limits of one reference range—that is, clearly normal—and outside the 97% limits of the other—that is, much more likely to be abnormal. Only 18 patients (0.9%) gave such a discordant classification. The clinical records, including treatment and subsequent course, and other biochemical data (serum thyrotrophin and triiodothyronine concentrations and repeat measurements of FTI) suggested that the modified FTI was more likely to be correct in 11 patients and the conventional FTI in four. There was insufficient evidence in the remaining three.

Comment

Over 99.9% of T4 in serum is protein bound, and the concentrations of binding proteins are affected by a wide variety of factors.^{3,4} Both THBC and TBG have been used to allow for changes in protein binding. Burr *et al*⁵ found that the ratio of T4 to TBG correlated better with thyroid state than the conventional FTI, but euthyroid patients with low values of THBC were not investigated. The T4:TBG ratio makes no allowance for changes in the other two binding proteins, thyroxine-binding prealbumin and albumin, which together bind about 30% of serum T4, and it cannot be used when TBG is absent. Further investigation is required to determine whether the T4:TBG ratio or our modification of the FTI provides the better discriminant for the evaluation of thyroid function in patients with abnormal binding proteins.

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¹ Goolden, A W G, Gartside, J M, and Sanderson, C, *Lancet*, 1967, **1**, 12.

² Clark, F, and Brown, H J, *British Medical Journal*, 1970, **2**, 543 and 672.

³ Oppenheimer, J H, *New England Journal of Medicine*, 1968, **278**, 1153.

⁴ Ingenbleek, Y, *et al*, *Clinica Chimica Acta*, 1975, **63**, 61.

⁵ Burr, W A, *et al*, *British Medical Journal*, 1977, **1**, 485.

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University Department of Medicine and Department of Chemical Pathology, St James's University Hospital, Leeds LS9 7TF

P SHERIDAN, MB, MRCP, lecturer and honorary consultant physician

K E NEWTON, MSc, senior biochemist

R B PAYNE, MD, FRCPath, consultant chemical pathologist