severe mental impairment motor development may not be significantly slower than other aspects of behaviour maturation. For this reason, any child with retarded milestones of development should be examined for evidence of cerebral palsy.

Types of Cerebral Palsy

The classical signs and symptoms of cerebral palsy found in older children are not usually present in the infant. True spasticity, for example, is rarely seen before the age of 3½ or 4 months and even in children who later show classical dyskinesia with marked unwanted involuntary movements, poverty of movement generally associated with generalized hypotonia is the striking feature (Fig. 1). The clinical picture found in later childhood is reached only gradually as the child matures, and various patterns of development have been described. In early infancy patients who suffer from congenital hemiplegia tend to move the limbs on the affected side less than the normal limbs, and the hemiplegic hand tends to remain closed after voluntary movement of the other hand has been observed (Fig. 2). In the first few weeks after birth there is commonly hypotonia rather than hypertonia in the affected limbs, but after 10 to 12 weeks increased resistance to full supination of the affected forearm when the elbow is extended can be appreciated.

In diplegia there is relative poverty of movement in the lower limbs and frequently there is generalized hypotonia. From the age of 6 or 8 weeks, however, there is a tendency for the lower limbs to extend at the knees and "scissor" with the toes pointing downwards when the patients are held in the erect position (Fig. 3). As they grow older the diplegic patients show steadily increasing and more constant rigidity in the lower limbs.

In ataxic cerebral palsy, "floppiness" and generalized poverty of movement are what the parents usually complain about first, and on examination hypotonia with hyperextensibility of joints are the striking findings. In dyskinesia there is also poverty of movement, often associated with hypotonia. The parents' first complaint is often about their baby's poor head control and the jerkiness of movement once he begins to reach out for objects. On examination gross fluctuation of muscle tone and posture are found when the baby tries to move and also on passive movement.

Associated Abnormalities

As indicated above, retardation of linguistic, adaptive, and social behaviour in patients suffering from cerebral palsy is more often the result of associated mental retardation than of specific disease of the motor apparatus. Other more specific abnormalities may be the result of disorders associated with cerebral palsy. Impairment of high-tone hearing is found in a high proportion of patients suffering from dyskinesia, the result of neonatal hyperbilirubinaemia. The finding or even suspicion that a patient may suffer from high-tone hearing loss should lead to full neurological examination.

A high proportion of patients suffering from hemiplegia, bilateral hemiplegia and diplegia, and ataxic diplegia have epileptic seizures.

Associated autonomic involvement, particularly in hemiplegia, sometimes results in the hand and foot becoming blue and showing oedematous swelling in cold weather; this may be the first observation which results in a diagnosis of hemiplegia being made, particularly in the Scottish climate. Similarly, in children suffering from mild congenital hemiplegia it may be the associated dwarfing of the affected limbs that the parents notice before the paresis of movement.

[*The second part of this article will appear in next week's issue.*]

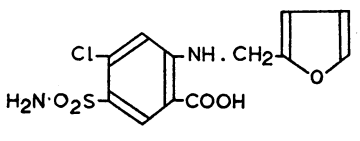
TO-DAY'S DRUGS

Frusemide

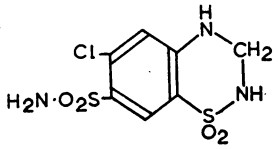
Frusemide is a new and powerful diuretic developed by Farbwerke Hoechst in Germany and marketed under the trade name of Lasix.

Chemistry

Many benzothiadiazine analogues have been introduced into therapeutics since the discovery of chlorothiazide by Novello and Sprague in 1957.[1] Frusemide (4-chloro-*N*-(2-furyl methyl)-5-sulphamoylanthranilic acid) is a new analogue, the chemistry of which differs in that the thiadiazine ring has been replaced by a furfuryl group substituted on the amino nitrogen of the anthranilic acid. The basic similarity of the two structures can be seen by comparing frusemide and hydrochlorothiazide in the figure.



FRUSEMIDE



HYDROCHLOROTHIAZIDE

Pharmacology

Existing thiazide diuretics vary greatly in their potency per unit of weight. Thus 1 mg. of polythiazide is approximately equivalent to 500 mg. of chlorothiazide. However, if dose-response curves in animals are plotted for a variety of benzothiadiazine diuretics the maximal response is similar for all of them. Frusemide is quite different in that it can produce more than twice as much urinary sodium excretion at its maximal dose than any of the benzothiadiazines.[2] In this respect frusemide resembles another new diuretic, ethacrynic acid.[3] Stop-flow experiments in dogs show a decreased sodium and potassium reabsorption in the proximal tubule and decrease of sodium reabsorption in the distal tubule.[4] Micropuncture studies on single nephrons in cat kidneys also indicate an action in the proximal tubule and also in a more distal site, possibly the loop of Henle.[5]

Clinical Pharmacology

Dose-response curves in normal human volunteers confirm that the maximal natruretic activity of frusemide is considerably greater than the maximal activity of hydrochlorothiazide. The

duration of action of frusemide is short and after a single oral dose most of the effect has gone within four hours. The duration of action of benzothiadiazine diuretics varies, but that of hydrochlorothiazide is between 12 and 18 hours.

It is important to be clear about terms used in the discussion of the effects of diuretic drugs. The potency of the compound is often referred to in terms of equiactive dose and in these terms frusemide, milligram per milligram, elicits about the same response as hydrochlorothiazide. The maximal effect, sometimes referred to as efficacy, is quite different. In the sense of natruretic activity frusemide is a more efficacious drug than hydrochlorothiazide. Another term which also causes confusion is the sodium/potassium ratio in the urine. This term is almost completely meaningless unless information is also given about the daily sodium/potassium intake and the previous diuretic history of the patient. For example, most drugs, such as the benzothiadiazines, which cause sodium and some potassium loss will cause a lower sodium/potassium ratio when they are given in high doses than in low ones. This is simply because as the dose is increased relatively more potassium than sodium comes out in the urine.

The manufacturers of frusemide claim that it causes relatively less potassium loss in the urine than benzothiadiazine diuretics. Judgment on this claim must be reserved until more evidence is available.

Clinical Use

Frusemide is formulated in 40-mg. tablets for oral administration and ampoules containing 20 mg. of the drug in 2 ml. are available for parenteral use.

The clinical indications for its use are similar to those for the other effective oral diuretics. While experience is being gained it may be wise to reserve frusemide for those patients who show an incomplete response to other diuretics, but in principle the compound can be used for any purpose for which benzothiadiazines have been prescribed. Thus congestive heart failure, nephrotic syndrome, cirrhosis, and hypertension will be the main indications.

The manufacturers state that the dose may safely be increased up to 500 mg. daily, but the usual dose is 40–120 mg. daily. The starting dose of frusemide is 40 mg. once or twice daily, and this should be increased slowly if the lower dose proves inadequate. It would be most unwise to begin treatment with a very large dose. Diuretics can be dangerous and even bring about death of patients by sudden alteration in water and electrolyte metabolism if they are misused.

There is convincing published evidence that frusemide may sometimes prove effective when benzothiadiazine diuretics such as hydrochlorothiazide have failed.[6]

Potassium depletion may occur when frusemide is used in a large dose, and further comparative studies are needed to establish whether it has any substantial advantage over hydrochlorothiazide in this respect. At present it should be standard practice to check serum potassium when patients are on frusemide, and those at special risk, such as cirrhotics, should receive routine potassium supplements.

Parenteral Therapy

Intravenous doses of frusemide (20–60 mg.) have a prompt but very short duration of action. They may prove useful in the treatment of acute pulmonary oedema. The intramuscular route is effective and painless if venepuncture is difficult.[6]

Toxicity

The acute oral toxicity of frusemide is low, being of the order of 2–4 grammes per kilogram in dogs and rats. Chronic toxicity studies in rats and dogs showed some deaths when the daily dose was as high as 350–400 mg. per kilogram. The animals which died showed degeneration of the myocardial fibres and renal changes which included calcification. A reversible elevation of the blood urea occurred in these animals, probably as a result of sodium depletion. The changes in the heart and kidneys at these very high dose levels probably result from potassium depletion, but the manufacturers do not give the values of serum potassium in their drug toxicity report.

Side-effects

Apart from sodium and potassium depletion, which are inherent in the diuretic activity, few side-effects have been reported. In particular there have been no instances of hypersensitivity or blood dyscrasia. Precipitation of gout has occurred, but this can happen with any diuretic. There have so far been no reports of diabetogenic activity, but this uncommon effect of benzothiadiazines was not generally recognized until they had been in use for several years.

Place in Therapy

It is too early to form any general judgment about the usefulness of this drug. If no important toxic or side-effects are revealed by wider experience, it should prove a useful addition to the diuretic armamentarium. It is genuinely more efficacious than the thiazides and seems to share their low toxicity. It has a rival in ethacrynic acid, which has a completely different structure, but the relative usefulness of the two substances is not yet known.

A very potent drug such as frusemide should not be used if a milder one such as hydrochlorothiazide is effective.

As the efficacy of diuretics improves so do their potential dangers ; it is important to exercise caution and begin at a low dose.

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