CARBONIC ANHYDRASE INHIBITORS AND OSMOTIC AGENTS IN GLAUCOMA

CARBONIC ANHYDRASE INHIBITORS

Several carbonic anhydrase inhibitors (CAI) are now available and, although their mode of action is similar, some patients can tolerate one of these drugs yet not another, and some fail to respond to one yet their ocular tension can be controlled by another. CAIs inhibit the secretion of aqueous, probably by a direct action on the ciliary epithelium.

Acetazolamide (Diamox)

The ability of acetazolamide to lower the ocular tension has led to its widespread use in all forms of primary and secondary glaucoma. Its use has also been advocated to restore post-operative flat anterior chambers, to reduce the incidence of post-operative hyphaema, and to reduce papilloedema and post-operative and inflammatory retinal oedema, although the evidence for its efficacy in some of these conditions is slight.

As acetazolamide reduces the secretion of aqueous, it may be used in simple glaucoma together with cholinergic and anti-cholinesterase drugs, the main effect of which is to increase the facility of aqueous outflow. The pressure-lowering effect of the combined use of acetazolamide and the miotics is greater than that of each used alone. Acetazolamide and local adrenaline also have an additive effect in reducing the ocular tension. The rate of aqueous formation is reduced by about 50 per cent. by acetazolamide and by about 30 per cent. by local adrenaline; the two drugs together reduce it by about 66 per cent.

Acetazolamide is particularly valuable combined with miotics and osmotic agents in the pre-operative treatment of acute closed-angle glaucoma, and combined with mydriatics and steroids in the management of hypertensive uveitis.

Dosage: Acetazolamide is usually given orally in doses of 125 to 500 mg. two to four times a day (250 mg. tablets). After a single dose its action is apparent in from 60 to 90 minutes, reaches a maximum in 3 to 4 hours, and has worn off in 6 to 12 hours. A long-acting preparation containing 500 mg. acetazolamide (Diamox Sustets) has an effect lasting 12 to 18 hours. Acetazolamide is the only CAI that can be given intravenously; its effect on the ocular tension commences within a few minutes and reaches a maximum in $\frac{1}{2}$ to 4 hours. Infants tolerate acetazolamide well with minimal side-effects; the dose is 5 to 10 mg./kg. body weight 4 to 6-hourly.

Methazolamide (Neptazane)

This CAI is excreted from the body more slowly than acetazolamide and its effect on the ocular tension appears to take place more slowly and lasts somewhat longer. It is more potent than acetazolamide and causes less frequent renal calculi as it does not depress urinary citrate.

Dosage: 50 to 100 mg. three to four times a day (50 mg. tablets).

Dichlorphenamide (Daranide)

This drug has the same side-effects as acetazolamide, for which it is a useful substitute, except for a lesser tendency to cause dermatitis, renal calculi and metabolic acidosis. It may induce a more pronounced renal loss of potassium.

Dosage: 50 to 200 mg. three to four times a day (50 mg. tablets).

Ethoxzolamide (Cardrase)

This has the same side-effects as acetazolamide but at a lower dosage.

Dosage: 125 to 250 mg. four to six times a day (125 mg. tablets).

Side-effects of CAIs

A transient myopia may occur. Systemic side-effects are common but not usually serious; these include parasthesiae, loss of weight, nausea, anorexia and fatigue. The side-effects necessitating discontinuation of the drug are ureteric colic, exfoliative dermatitis, agranulocytosis, and severe gastro-intestinal upsets. The formation of renal calculi may be related to the marked decrease in the excretion of urinary citrate without a corresponding fall in calcium excretion. Some patients who develop ureteric colic while on acetazolamide can tolerate smaller doses of methazolamide, although the latter tends to produce more malaise and fatigue. The administration of potassium bicarbonate is believed to increase the action of carbonic anhydrase inhibitors.

OSMOTIC AGENTS

Agent	Urea	Mannitol	Glycerol
Preparation	30 per cent. solution in 10 per cent. invert sugar	20 per cent. solution in water	50 per cent. solution in water, fruit juice to flavour
Dosage	0.5-2.0 g./kg. body weight	0.5-2.0 g./kg. body weight	0.75-1.5 g./kg. body weight
Administration	Intravenous 60 drops/min.	Intravenous 60 drops/min.	Oral
Maximum Activity	$\frac{1}{2}$ hour	$\frac{1}{2}$ hour	1 hour
Duration of Action	4-6 hours	4-6 hours	3 hours
Fall in Ocular Tension	+++	+++	++
Fate in Body	(small molecule) Enters cells Penetrates eye 50 per cent. reabsorbed by renal tubules	(large molecule) Stays extracellular Does not penetrate eye Neither secreted nor reabsorbed by tubules	(large molecule) Stays extracellular Does not penetrate eye Metabolized to sugar 10 per cent. excreted in urine
Cellular Dehydrating Effect	—	++	++
Diuretic Effect	++	+++	+
Side-effects	All osmotic agents may produce headache, backache, nausea, vertigo, and mental confusion. Potassium loss may occur.		
	Urinary retention Congestive cardiac failure Pulmonary oedema Sloughing of skin Venous thrombosis	Urinary retention Congestive cardiac failure Pulmonary oedema	Severe nausea and vomiting
Contraindications	All osmotic agents must be used with extreme caution in patients with cardiac, renal, or hepatic disease In elderly patients use the minimum dose required to produce the desired effect.		
		Cardiac failure Dehydration	Diabetes (unless covered by insulin)

CHOICE OF OSMOTIC AGENT IN PARTICULAR CASES

Agent	Urea	Mannitol	Glycerol
Vomiting	+++	++	—
Dehydration	+++	—	+
Cardiovascular Disease	+	—	++
Diabetes	+++	+++	— (unless covered by insulin)
Inflamed Eye	+	+++	++

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