high in acromegaly and low in panhypopituitarism or isolated growth hormone deficiency, rising after the injection of HGH. Hall and Uthne[23] have reported that the plasma levels of sulphation factor in growth-hormone-deficient patients receiving continuous HGH therapy are directly proportional to the rate of gain in height.

If plasma sulphation factor concentration does not rise with HGH therapy, no acceleration of height velocity occurs. This point is best illustrated by the type of dwarfism first described by Laron and his associates.[24] The defects of growth are identical to those of isolated growth hormone deficiency, but the plasma level of immunoassayable growth hormone is above normal. Nevertheless, the level of sulphation factor is very low and fails to rise with prolonged HGH therapy, which does not accelerate the rate of gain in height.[25]

Therefore, it appears that growth hormone belies its name. It is one item on a metabolic list of growth-promoting factors that allow an adequate expression of a rate of gain in height that may be genetically determined. It probably has no direct effect on skeletal growth, its target again being the liver. If there is a long-term homoeostatic mechanism linking growth hormone with growth, it is likely to link the plasma level of sulphation factor with the growth-hormone-releasing factor of the hypothalamus.

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Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Respiratory Stimulants

British Medical Journal, 1972, **2**, 522–523

The story of respiratory stimulants has been repeatedly one of initial enthusiasm followed by gradual disillusionment. This is partly because they have been widely advocated for conditions in which they are not helpful and may be dangerous: neonatal asphyxia,[1] postanaesthetic apnoea, and drug overdosage.[2] And yet an effective respiratory stimulant is needed, particularly for some patients with acute respiratory failure when the alternative may be mechanical ventilation, which, in these patients, carries an appreciable mortality. The indications in patients with chronic respiratory failure are much less clear.

Uses

ACUTE RESPIRATORY FAILURE.

For patients who are hypercapnic, drowsy, and unable to cough adequately a respiratory stimulant is essentially "buying time"—the time necessary to allow other treatment, such as antibiotics, to be fully effective. The greatest need is to keep the patient awake and alert and thus able to cough effectively and remove bronchial secretions.

CHRONIC RESPIRATORY FAILURE.

Though patients may occasionally benefit, the rationale behind giving long-term respiratory stimulants to patients with chronic respiratory failure is very much open to question. A respiratory stimulant will increase both minute ventilation and the work of breathing, which causes an increase in oxygen consumption and carbon dioxide (CO_2) production by the respiratory muscles. Arterial P_{CO_2} depends on the balance between CO_2 production and alveolar ventilation, and as both will be increased by respiratory stimulants there may be little change in arterial P_{CO_2} despite an increase in ventilation.

Contraindications

Respiratory stimulants should not be given to certain patients. Firstly, in conditions where hypoxaemia is not associated with hypercapnia—for example, asthma. If the arterial P_{CO_2} is normal or low then ventilatory drive is adequate and respiratory stimulants will do no good and may be harmful. Secondly, patients with respiratory failure due to neurological or muscular disease; and, finally, great caution should be taken in patients with epilepsy or coronary artery disease.

Br Med J: first published as 10.1136/bmj.2.5812.522 on 27 May 1972. Downloaded from http://www.bmj.com/ on 13 March 2024 by guest. Protected by copyright.

Mode of Action

Most of the drugs called respiratory stimulants act directly on the respiratory centre. They do not, however, act *specifically* on the respiratory centre and many of their side effects are due to general stimulation of the central nervous system.

The carbonic anhydrase inhibitors are used less frequently and they act indirectly on the respiratory centre. Their main action is to increase renal excretion of bicarbonate thus producing an acidosis which will stimulate the respiratory centre. These drugs will be effective only when the patient can increase his alveolar ventilation. They are dangerous in acute respiratory failure, when they will only aggravate the acidosis already present. The inhibition of carbonic anhydrase in the red cell impairs CO_2 transfer from the tissues so that the fall in tissue P_{CO_2} may not be as great as the fall in arterial P_{CO_2}.

Drugs Available

PARENTERAL PREPARATIONS

Nikethamide has been widely used in respiratory failure and is usually given by intermittent intravenous injection. As its action lasts less than two minutes the patient is encouraged to cough vigorously as soon as the injection has been given. A dose of 2 ml is usually given initially and this may then be increased to achieve the optimum dose which will alert the patient without producing appreciable side effects. Unfortunately, most patients do not remove much sputum in this time and after a few minutes they lapse back to their original state. Nevertheless, the occasional drowsy patient will clear secretions and obtain long-term benefit in terms of increased alertness and improvement in blood gas tensions. Unless this benefit is achieved, however, nikethamide should not be continued. Intravenous infusion of nikethamide is unsatisfactory because side effects are almost invariable if a therapeutic level is achieved and intramuscular injections are less effective.

Amiphenazole, ethamivan, and prethcamide are similar to nikethamide and are also given by intermittent intravenous injection or intravenous infusion. There is little evidence to support claims that any of these four respiratory stimulants has any appreciable advantage over the other three. Similar side effects are encountered with all four drugs—skin irritation, anxiety, sweating, gastrointestinal upset, twitching, and generalized convulsions. Doxepram is prepared as an intravenous infusion and the only common side effect is a feeling of warmth if the rate of infusion is increased. A therapeutically effective dose appears to be easier to maintain without unpleasant side effects with doxepram than with the other respiratory stimulants.

Names and Dosage of Some Respiratory Stimulants in Current Use

Name	Dosage	
	Infusion Rate (mg/min)	Single Injection (mg)
Ethamivan (Vandid) ..	20	150-400
Doxepram hydrochloride (Dopram)	2	—
Nikethamide (Coramine) ..	20	25% solution 2-10 ml (50-250 mg)
Prethcamide (Micoren) ..	20	225-450
Amiphenazole (Daptazole)	10	150-400
Carbonic Anhydrase Inhibitors	Oral	
Dichlorphenamide (Daranide)	25 mg b.d. for 1 week, then 50 mg b.d.	

The doses given are only intended as general guide lines for an average 70-kg man as there are large individual differences in response to these drugs.

ORAL PREPARATIONS

Amiphenazole, ethamivan, and prethcamide may be given orally for patients with chronic respiratory failure, but the results have been very disappointing and side effects have been troublesome.

Acetazolamide is a weak carbonic anhydrase inhibitor which tends to produce a hyperchloraemic acidosis. Dichlorphenamide—another oral preparation—is more potent and causes less chloride retention but it has been found to produce either headache or gastrointestinal symptoms in many patients.

Efficacy

All of these drugs increase minute ventilation and lower arterial P_{CO_2} in many patients with respiratory failure but there have been two main problems. Firstly, most of the drugs have been given as intermittent injections, so that their actions have been very short-lived. Undoubtedly, patients do occasionally benefit from a single injection but on the whole this short action has severely limited their usefulness. The second important problem has been the frequency of side effects. Most studies have shown only a narrow margin between a therapeutically effective dose and that which produces unpleasant side effects. Doxepram hydrochloride has possible advantages over the other respiratory stimulants in that it can easily be given by continuous infusion to produce a maintained effect and the ratio between a therapeutic dose and troublesome side effects appears to be less.[3]

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