

## Van die Redaksie / Editorial

### Non-pharmacological therapy for recurrent tachycardia

Tachyarrhythmias may be secondary to a generalised process such as thyrotoxicosis, drug intoxication, or electrolyte imbalance; it may be an expression of cardiac failure or result from a specific process within the heart (primary arrhythmias). The mechanism of such primary arrhythmias may be mainly anatomically based, such as occurs with accessory pathways and ventricular aneurysm, or functional, reflecting, for example, the effects of increased sensitivity of specific areas within the heart to the normal fluctuation in circulating catecholamines. It is in the area of primary arrhythmias that the physician has traditionally tried varieties of drugs, often on a somewhat empirical basis with variable (often unknown) degrees of success. The development of safe open-heart surgery combined with a better understanding of the mechanisms of supraventricular tachycardias in the Wolff-Parkinson-White (WPW) syndrome inspired Sealy in 1968 to undertake isolation and division of accessory pathways. The resultant freedom from recurrent episodes of tachycardia without the use of drugs associated with the loss of the delta wave, the hallmark of WPW, ushered in the era of anti-arrhythmic surgery.

The role of pharmacological therapy for chronic recurrent tachyarrhythmias is basically prophylactic and based on the proposition that the effective agent will either suppress the initiating process or prevent perpetuation of the arrhythmia. Non-pharmacological methods act either by preventing the arrhythmia by removing the basic anatomical substrate (thus offering the possibility of a cure), or by interacting with the process once the arrhythmia has developed, a rescue action as typified by the implantable defibrillator. Specific alteration of a relatively large and localised arrhythmogenic environment has been promised by left stellate ganglion resection in patients with recurrent syncope and prolonged QT syndromes.

Pharmacological therapy has been with us for a long time, is by and large non-invasive and is freely available. It is what we have been used to. Among the important problems with pharmacological therapy is the fact that it acts via systemic drug delivery for a highly localised problem. Generalised side-effects are thus a frequent accompaniment. An example of this is the excess of 17% incidence of serious systemic side-effects requiring cessation of treatment for amiodarone therapy for important, usually life-threatening arrhythmias.<sup>1</sup> Most potent anti-arrhythmic drugs are aninotropic and are frequently dangerous when given to patients with concomitant mechanical cardiac dysfunction. The results of the recent

CAST study<sup>2</sup> highlighted the danger of empirical anti-arrhythmic therapy for patients with varying degrees of ventricular ectopy and non-sustained ventricular tachycardia after myocardial infarction. In this study, the use of type IC drugs, i.e. flecainide and encainide, was associated with a higher mortality than placebo. This high mortality probably related to their propensity to produce arrhythmias as well as the low mortality from the ventricular arrhythmias being treated. Indeed, it is only when drug therapy is guided by repeated challenge by invasive programmed stimulation of the ventricle that the incidence of recurrent ventricular tachycardia has been shown to be favourably affected.

It is difficult to be sure of the costs of each prescription for anti-arrhythmic therapy. Many potent anti-arrhythmic drugs are extremely expensive when given in a dose likely to be effective for major chronic recurrent arrhythmias such as ventricular tachycardia or atrial fibrillation with rapid ventricular response in patients with a functioning accessory pathway. On the other hand, correct utilisation of, for example,  $\beta$ -blocking drugs or digitalis can be highly cost-effective.

Non-pharmacological methods of therapy include ablation of accessory pathways, resection of ventricular aneurysms, excision of automatic, usually atrial, foci, physical ablation or modification of the atrioventricular node and the use of devices such as the anti-tachycardia pacemakers and implantable defibrillators. There has been outstanding success with ablative techniques, particularly to accessory pathways, and with implantable defibrillators. Ablation of accessory pathways may be surgical or may utilise transcatheter techniques. The success rate for surgical ablation in a number of centres is so high and the mortality and morbidity so low, that the indications for surgery have been broadened virtually to include all symptomatic patients with the WPW syndrome. Indeed, in the face of these results, it is becoming more difficult to justify a pharmacological approach. The choice will of course widen further once transcatheter ablative techniques have been perfected. Such techniques will offer an attractive alternative to life-long pharmacological therapy.

In this issue (p. 583) Scott Millar and colleagues report the current status of surgery for accessory pathways at Groote Schuur Hospital. Their results are similar to those reported earlier from other institutions, who have now attained near 100% success with extremely low morbidity and mortality.<sup>3</sup> The authors have clearly defined the problem areas and the steps necessary to



overcome them. We are encouraged that these necessary steps are well within their capabilities. The excellent status of their successful cases and their clear and extremely encouraging commitment to this problem augur well for future results. We look forward to these and similar approaches in other specialised institutions.

On a par with the success of WPW surgery has been that obtained with implantable automatic cardioverter-defibrillators for recurrent ventricular fibrillation and haemodynamically unstable ventricular tachycardia. The life survival figures for high-risk patients with life-threatening arrhythmias receiving these devices is greater than 98% at 1 year and 94% at 5 years in two major series<sup>4,5</sup> and the number of implants is therefore growing exponentially. Newer devices are extremely sophisticated, not only capable of diagnosing and automatically treating ventricular fibrillation or ventricular tachycardia, but also offering various forms of anti-tachycardia pacing, cardioversion and cardiac pacing in a programmable sequence. Seven such devices have been implanted in South Africa to date, some via the transvenous route. We await the long-term results of local experience. Transcatheter ablation of the atrioventricular node with pacemaker implantation for drug-resistant supraventricular tachycardias has to my knowledge been performed in 3 centres in South Africa, with reasonable results. Internationally the results of such transcatheter ablative techniques are improving both in regard to efficacy and

lack of morbidity and mortality. Much of this relates to technological advances in energy delivery systems.

Choosing appropriate therapy for individual patients at a particular point in time is an ongoing challenge. In the field of primary recurrent tachyarrhythmias there is no doubt that there will be a growing role for non-pharmacological methods. *Pari passu* with this has been the realisation that accurate diagnosis and understanding of the natural history of specific arrhythmias is essential for such choice to be rational and, as the CAST study has shown us, safe. Currently non-pharmacological methods are largely reserved for patients in whom drug therapy has either failed or is unacceptable. In this era of technological advance we can look forward to more refined and specific forms of non-pharmacological therapy for patients with recurrent tachyarrhythmias and consequently freedom from drug side-effects. Ablative techniques offer, at last, a prospect of cure.

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## Alpha-adrenergic agonists in anaesthesia and analgesia

Alpha-2-adrenergic receptors are present in the central nervous system in both presynaptic and postsynaptic locations,<sup>1</sup> and there has recently been substantial interest in the anaesthetic and analgesic properties of  $\alpha_2$ -adrenergic agonists. Activation of the  $\alpha_2$ -adrenergic receptors produces many physiological effects, including anxiolysis, sedation, decreased salivary secretions, bradycardia, lowered blood pressure (reduced sympathetic flow), hypothermia, and mydriasis.<sup>2</sup> Given their desirable physiological profile,  $\alpha_2$ -agonists could be useful anaesthetic and analgesic adjuvants. Surgical procedures, endotracheal intubation, and anaesthesia are stressful. They may induce potentially harmful reactions, such as increases in the secretion of catecholamines and other stress hormones, and increases in heart rate and blood pressure.<sup>3</sup> Effective attenuation of the sympatho-adrenal stress responses is an important goal in modern anaesthesia, especially in patients with hypertension and coronary artery disease. The  $\alpha_2$ -agonists may play an important role in this regard.

The  $\alpha_2$ -agonists include drugs such as clonidine, medetomidine, and azepexole. Clonidine has a longer

plasma elimination half-life (7,7 hours) compared with dexmedetomidine (2,3 hours).<sup>3</sup> It is 10 - 100 times less selective for the  $\alpha_2$ -adrenergic receptor than dexmedetomidine, and is known to have a ceiling effect that limits its anaesthetic action.<sup>1</sup> This may be due to its  $\alpha_1$ -agonist properties, which manifest themselves at higher doses. Medetomidine is a 1:1 racemic mixture of optical isomers of which the *d*-isomer, dexmedetomidine, is pharmacologically active.<sup>3</sup> It is a more effective  $\alpha_2$ -agonist than clonidine in most pharmacological models tested so far. Another selective  $\alpha_2$ -agonist, azepexole, has similar anaesthetic properties to dexmedetomidine.<sup>2</sup>

The advantages of  $\alpha_2$ -agonists include lack of major respiratory depression and addiction, and lack of other opioid side-effects, such as nausea, vomiting, or pruritus.<sup>4</sup> Disadvantages include hypotension, bradycardia, and a drop in cardiac output. The reduction in the activities of the sympathetic nervous system can be reversed by  $\alpha_2$ -antagonists (idazoxan, atipamezole, and yohimbine).<sup>4</sup> They decrease heart rate by direct cardiac as well as central mechanisms, and may decrease velocity through the cardiac conduction system.<sup>5</sup> Caution is needed in



patients with pre-existing conduction disturbances. Hypotension can occur due to a brainstem-mediated inhibition of sympathetic and enhancement of parasympathetic activity.<sup>5</sup> The dose of  $\alpha_2$ -agonist must therefore be carefully assessed. With clonidine (at high doses), this lowering of blood pressure is balanced by its direct vasoconstrictor action on peripheral blood vessels. In humans (unlike animal studies), serum glucose, cortisol and arterial oxyhaemoglobin saturation seem unaffected by  $\alpha_2$ -agonists after chronic systemic and acute epidural administration,<sup>6</sup> although acute systemic administration of clonidine may reduce serum glucose and cortisol levels.<sup>7</sup>

The  $\alpha_2$ -agonists have been used as premedicants. Oral clonidine and intravenous dexmedetomidine resulted in a significant reduction in fear and anxiety experienced.<sup>3,8,9</sup> Dryness of the mouth and sedation also occurred. Given as premedicants,  $\alpha_2$ -agonists have been found to reduce the sleep dose of induction agents needed (e.g. thiopentone,<sup>3</sup> methohexitone<sup>9</sup>).

By inhibiting sympathetic transmitter release,  $\alpha_2$ -agonists reduce catecholamine levels and improve haemodynamic stability during the induction and maintenance of anaesthesia.<sup>1,3</sup> They also reduce the amount of inhalational anaesthetic agents needed by acting on presynaptic and postsynaptic  $\alpha_2$ -adrenergic receptors in the central nervous system and inhibiting central noradrenaline release.<sup>3</sup> This is reflected by a lower MAC value.<sup>10</sup> Several investigators have proved  $\alpha_2$ -agonists to be anaesthetic-sparing agents with hypnotic and analgesic effects of their own.<sup>10</sup> They augment the peri-operative analgesia/anaesthesia produced by opioids,<sup>1,4</sup> and opioid dosage can thus be reduced. Dexmedetomidine can induce skeletal muscle relaxation, and may be clinically effective in preventing the muscle rigidity produced by moderate to high doses of opioids.<sup>2</sup>

The  $\alpha_2$ -agonists effect cerebral vasoconstriction by increasing cerebral vascular resistance due to stimulation of postsynaptic  $\alpha_2$ -adrenergic receptors located in cerebral vessels.<sup>1</sup> They may thus be useful adjunct agents in neurosurgery. Clonidine has been shown to decrease cerebral blood flow in healthy human volunteers.<sup>9</sup> Dexmedetomidine (in dogs) causes significant reduction in CBF without influencing the metabolic rate of oxygen.<sup>10</sup>

The  $\alpha_2$ -agonists are also analgesics when given epidurally and intrathecally. They block transmission of pain information by activating presynaptic and postsynaptic  $\alpha_2$ -adrenergic receptors in the spinal cord, which inhibit substance P release and dorsal horn neuron firing respectively.<sup>5</sup> Their lipid solubility and rapid absorption and elimination in the cerebrospinal fluid limit rostral spread. Epidural clonidine has an onset and duration of analgesia similar to that of epidural fentanyl.<sup>5</sup> The duration of analgesia may be prolonged by injection of large doses.<sup>5</sup> It is slowly absorbed into the systemic circulation (perhaps due to slow release from epidural fat). Peak plasma concentrations may not occur until more than 1 hour after injection.<sup>6</sup> Clonidine's short elimination half-life in the cerebrospinal fluid (43 minutes) suggests that accumulation is unlikely.<sup>6</sup> Clonidine is preservative-free and isotonic, with a pH of 4.0 - 4.5, making it suitable for epidural administration. Several animal studies have shown no direct neurotoxic effects.<sup>11</sup>

Epidural clonidine (600  $\mu$ g or more) is effective for acute postoperative pain.<sup>5</sup> The most common side-effect is hypotension. This occurs mainly from inhibition of sympathetic nervous activity in the spinal cord. It is more likely to occur following intrathecal administration in patients with pre-existing hypertension or with hypovolaemia.<sup>5</sup> Because clonidine may increase blood pressure by a peripheral action, hypotension is again lessened by increasing plasma concentrations.<sup>6</sup>

When  $\alpha_2$ -agonists are combined with opioids (clonidine and morphine) either epidurally or intrathecally, a shift of the opioid dose-response curve to the left occurs.<sup>12,13</sup> The combination produces greater analgesia than either alone, thereby reducing dose requirements, and delaying the onset of tolerance.<sup>12,13</sup> It has been found that low doses of both clonidine and morphine do not reduce wide dynamic range neuronal activity (in cats), whereas the combination of the two produced significant reductions.<sup>14</sup> This is borne out clinically as sub-analgesic concentrations of clonidine and morphine will potentiate one another. Combinations of  $\alpha_2$ -agonists, opioids, and local anaesthetic agents<sup>12,15</sup> (e.g. clonidine, fentanyl, bupivacaine) are now used for peri-operative anaesthesia and analgesia. Pain is then inhibited by three different mechanisms, resulting in a decrease in the dose of  $\alpha_2$ -agonist, opioid and local anaesthetic agent needed.<sup>16</sup> With the manufacture of microcatheters (28-32-gauge), intermittent or continuous intrathecal delivery of these combinations is now possible.<sup>17</sup>

The  $\alpha_2$ -agonists have been found to suppress shivering after epidurals with local anaesthetic agents.<sup>18</sup> Intravenous clonidine (150  $\mu$ g) has been found to reduce postoperative oxygen consumption.<sup>19</sup> Epidural clonidine (100 - 900  $\mu$ g) has been found to be effective in treating deafferentation or neurogenic pain in the cancer patient.<sup>6</sup> Effective analgesia can also be produced when tolerance to opioids has developed and epidural clonidine/morphine infusions have been successfully administered to cancer patients at home for up to 5 months.<sup>6</sup> Epidural clonidine has been successful in treating the pain in arachnoiditis and proctalgia fugax, and also in treating deafferentation pain following spinal cord injuries or peripheral nerve injuries.<sup>20</sup> (Oral clonidine has long been used in the treatment of migraine.) In conclusion, the  $\alpha_2$ -agonists have properties of great potential benefit to anaesthesia and pain control. They are already widely used as veterinary sedative-analgesics.<sup>21</sup> However, their advantages and limitations require further definition. The identification of subpopulations of  $\alpha_2$ -adrenergic receptors may provide new opportunities for the development of subtype-selective pharmacological agents with more specific therapeutic actions.

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## The high price of becoming a doctor

By its very nature, medical education is an expensive business which involves taking the cream of school leavers and putting them through a highly intensive syllabus for 6 years, during which time they are almost totally economically non-productive. Added to the cost of tuition is the cost of accommodation, food and transport as well as all the other expenses which are part and parcel of everyday living. However, as a paper by Colborn in this issue of the *SAMJ* shows (p. 616), what has always been a heavy financial burden is now becoming virtually unupportable except by the very affluent. The average indebtedness of 5th and 6th year students at UCT amounted to approximately R37 000 each, of which in the region of R21 500 will have to be repaid in cash, and the balance by various service strings which may be attached to the bursary. Not only does this have serious financial implications for the individuals involved, and their families, but it also has a direct effect on the kind of students who take up medicine, and the kind of doctors that they become. Anyone who qualifies in medicine saddled with an enormous debt will have only one thing in mind at the start of his or her professional career, and that is to make as much

money as soon as possible. However, to do so is not easy, given the low salaries customarily paid to newly-qualified doctors, and whether such motivation is desirable for someone starting out on a professional career is highly debatable.

As the paper by Colborn points out, the pattern of those applying for the M.B. Ch.B. course at UCT is changing, and presumably the same is happening at other universities. White applicants are fewer, and black applicants on the increase. In a country which is currently undergoing fundamental changes, and in which there have been far too few black doctors, this is a healthy trend, but whether those from the less affluent sector of the population will be able to shoulder the crippling cost of their medical education is open to question.

In an ideal world, anyone who possesses the necessary qualities to become a doctor, which should include a strong sense of vocation, should be enabled to pursue their medical studies without completing them in a virtually bankrupt state. The burden is now too heavy. Who will help to lift it?

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