ALPHA-2 AGONIST AND ANESTHESIA

Essay

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In Anesthesia and I.C.U.

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Introduction

Much of the action of the body in maintaining cardiovascualr, gastrointestinal, and thermal homeostasis occurs through the autonomic nervous system (NAS). The ANS is also our primary defense against challenges that homeostasis. It provides involuntary (outside of consiciousness) control and organization of both maintenance and stress responses. In the words of Claude Bernard, the nature through it provident to remove these important phenomena from the capariciousncess of an ignorant will. Activation of the sympathetic nervous system elicits what is traditionally called the "fight of flight" response, including redistribution of blood flow from the viscera to skeletal muscle, increased cardiac fucntion, sweating, salivation, and papillary dilation. The parasympathetic system governs activities of the body more closely associated with maintenance of fucntion, such as digestive and genitourinary fucntions. A major goal of anesthetic administration is maintaining optimum homeostasis in the patient, inspite of powerful challenges to a sometimes tenuous physiologic balance. The intelligent administration of anesthetic care to patients requires a knowledge of ANS pharmacology in order to achieve desirable interactions anesthetic with the involuntary control system and to avoid responses or interactions with deleterious effects. In addition, disease states may impair ANS fucntion to a significant extent and may thereby alter the expected responses to surgery and anesthesia. Last, possible negative effects of the human stress response have long been appreciated, and considerable effort has been expended in examining the possibility that modification or ablation of the stress response may improve perinoperative outcome.

Nerves are traditionally calssified the chemical transmitters they contain. Nerves containing Ach are called cholinergic, whereas those containing norepinephrine (NE) of EPI are called adrenergic.

Drugs mimicking the action of NE are referred to as sympathomimetic, whereas drugs inhibiting these effects of NE are called sympatholytic. NE is the transmitter acting at adrenergic nerves where as both EP and NE are rleased by the adrenal medulla. Adrenergic receptors have been indentifeid and subdivided into α-and β-receptors and further subdivide into α1 - α2 - β1 - β2 and so forth α2- Receptors are primarily located on the presynaptic membrane, whereas α1- receptors mediate smooth muscle vasoconstriction. β1- receptors are found primarily on cardiac tissue, and β2-receptors mediate smooth muscle relaxation in some organs. We define adrenergic neurons as follows:

1- Postganglionic sympathetic neurons.
2- Some interneurons.
3- Certain central neurons.

Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in humans for analgesia and sedation.

Dexmedetomidine is a selective alpha2 adrenoceptor agonist that has been approved for sedation in the intensive care unit setting. Dexmedetomidine provides sedation, anxiolysis, and analgesia. Studies with dexmedetomidine have demonstrated an ability to either eliminate or decrease the need for other analgesic medications such as opioids. Further, dexmedetomidine does not produce respiratory depression due to its non-opioid mechanism of analgesia. Patients who received

dexmedetomidine in the intensive care unit were observed to be rousable and alert when stimulated from sedation. Dexmedetomidine produces mild antihypertensive effects with predictable hemodynamic effects during administration in the intensive care unit setting.

Clonidine, the first to be developed and the best known of these agents, is a direct-acting alpha-adrenergic agonist with a strong preference for the alpha-2 receptor. It acts centrally to produce inhibition of sympathetic vasomotor ceters by inhibiting release of norepinephrine in the medulla. Sympathetic tone is reduced; thus decreasing systemic blood pressure.

Aim Of The Work

The aim of this study is to analyze the up date and renew about effect of dexmedetomidine and its use in anesthesia and ICU. Also, to study the use of clonidine in anesthesia.

شبيهات مستقبلات ألفا-٢ واستخدامها فى علم التخدير

رسالة مقدمة من

الطبيب/ إسلام على محمد شابوب

بكالوريوس الطب والجراحة

توطئة للحصول على درجة الماجستير فى التخدير والعناية المركزة

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SUMMARY

Today the therapeutic objective for administration of α2-adrenoceptor agonists has shifted from reduction of high blood pressure to various other applications, including the management of myocardial ischaemia and withdrawal symptoms in drug addicts. The development of highly specific α-adrenoceptor agonists with profound effects on vigilance and haemodynamics has created new interest for the use of α2-adrenoceptor agonists for use in anaeshtesia and intensive care medicine. α2-adrenoceptor agonists possess a variety of pharmacological properties that render them desirable as adjuncts in anaesthesia. Clonidine, an imidazoline, is the prototypal α2-adrenocptor agonist. It has a relatively slow onset (0.5 h) and an elimination half-life of 9-12 h. They highly specific α2-adrenoceptors-agonist dexmedetomidine was approved in the USA at the end of 1999 for sedation and analgesia in the intensive care unit (ICU). This drug shows unique characteristics: patients are sedated but remain rousable and able to cooperate with the hospital staff when stimulated. Moreover, in ICU therapy with dexmedetomidine, there is no evidence of respiratory depression at clinical concentrations, and the heamodynamic changes are both moderate and predictable.

The present data demonstrate that dexmedetomidine effectively prevents delayed neuronal death in CA3 area and in the dentate hilus in gerbil hippocampus when the management is started before the onset of ischemia and continued for 48 h after reperfusion. Inhibition of ischemia-induced norepinephrine release may be associated with neuroprotection by dexmedetomidine.

Dexmedetomidine possesses several properties that may additionally benefit those critically ill patients who require sedation. In spontaneously breathing volunteers intravenous dexmedetomidine caused marked sedation, with only mild reductions in resting ventilation at higher doses.

Furthermore, studies in humans revealed that short-term administration of dexmedetomidine did not induce significant changes in blood concentrations of rennin, vasopressin, atrial natriuretic peptide or hydrocortisone however it increased blood level of growth hormone.

CONCLUSION

Dexmedetomidine was found to be a safe drug in therapeutic doses, it blunts the cardiovascular response to intubation and to the changes occur during laparoscopic cholecystectomy and offers a good control on heart rate, blood pressure. It also found to be safe on respiratory profile and it decreases the halothane requirement intraoperatively. Dexmedetomidine also have insignificant effect on the recovery time and prolong the time to first request for postoperative analgesia. Increasing the dose of dexmedetomidine from 0.5μg/kg/h^{-1} to 1μg/kg/h-1, offers more precise control on the heamodylnamic profile without increasing the incidence of any unwanted complication.

ALPHA TWO AGONIST AND ANESTHESIA

Alpha 2-adrenocetor agonists are being increasingly used in anesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anesthesia and surgery; but also cause sedation and analgesia. They are also used as adjuvant during regional anesthesia.

Alpha 2 receptors are found in the peripheral and central nervous system, platelets, and many other organ, including the liver, pancreas, kidney, and eye. Stimulation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses from other organs include decreased salivation, decreased secretion, and decreased bowel motility, inhibition of rennin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney, decreased intraocualr pressure; and decreased insulin release from the pancreas *(1)*.

In high doses, alpha 2-agonists have the potential for causing both systemic and pulmonary hypertension and direct of reflex bradycardia. In the lower, clinical range, alpha 2-agonists infusions decreased blood pressure, presumably as a result of a central sympatholytic effect. At higher plasma levels, peripheral alpha 2-receptor mediated vasoconstriction overrides the sympatholytic effects, resulting in increased pulmonary artery and systemic blood pressure. In healthy patients with intact baroreflexes, this can lead to bradycardia. Reflex bradycardia in conjunction with the vagal mimetic property of alpha 2-agonists could lead to severe bradycardia or asystole.

A variety of perioperative effects of alpha 2 agents have been studied. These include effects on the stress response to surgery; myocardial ischemia; sedation, axiolysis, and analgesia; hemodynamics; prevention of delirium, and mitigation of drug withdrawal.

Sedation, anxiolysis, analgesia:

One of the highest densities of alpha 2-adrenoceptor has been detected in the pontine locus ceruleus (LC), a key source of noradrenergic innervation of the fore-brain and an important moedulaor of vigilance. The sedative effects of alpha 2-adrenoceptor activation have been attributed to the inhibition of this nucleus. After dexmedetomidine binds to alpha 2-adrenoceptors in the LC, transmembrane signaling results in activation of an inwardly rectifying potassium channel facilitating a K^+ efflux and inhibition of voltage-gated Ca^{2+} channels. The resulting hyperpolarization decreases the firing rate of LC neurons and allows presynaptic inhibition of their terminals. Hyperpolarization of noradrenergic LC neurons appears to be a key factor in initiating the anesthetic mechanism of action of dexmedetomidine *(8).*

Control of haemodynamic instability and prevention of myocardial ischaemia and related cardiac complications

The haemodynamic effects of alpha 2-adrenergic agonists are both peripheral and central. Stimulation of subendothelial receptors causes vasoconstriction *(8).*

Conversely, stimulation of a2-adrenergic receptors of neurons in the nucleus tractus solitarius, augments the inhibition by this nucleus of the sympathetic neurons of the medulla *(8).* In this way, alpha adrenergic agonists reduce the tonic activity of the baroreflex, decreasing arterial pressure and causing bradycardia. On the other hand the phasic activity of

the baroreflex is preserved on even improved, so that any decrease in arterial pressure is followed by a significant increase in heart rate and any increase in arterial pressure is followed by a significant increase in heart rate and any increase in arterial pressure is better controlled by a consequent bradycardia *(9)*. In addition, a2-adrenergic agonists depress presynapic sympathetic nerones in the lateral horn of the thoracic spinal cord. This effect is reversed by the local administration of cholinesterase inhibitor neostigmine ***(10).*** Consequently, intrathecal administration of a2-adrenergic agonists causes more marked hypotension than parenteral administration ***(11).*** Finally, hypotension and bradycardia induced by a2-adrenergic agonists are reversed by ephedrine and atropine respectively but large doses are required.

In both healthy volunteers and patients, a2-adrenergic agonists decrease plasma catecholamine levels. Giving a2-adrenergic agonists before anaeshtesia decreases cardiac output, vascular resistance, cardiac preload, afterload and contractility *(8)*. Conversely, during anaeshtesia, clonidine increase cardiac output by improving cardiac loading conditions ***(12, 13).*** In addition a2-adrenergic agonists prevent hypertension and tachycardia on intubation and during surgical stimulation ***(12, 13).*** However hypertension and bradycadia occur more frequently in patients after clonidine ***(12, 15).*** During recovery from anaeshtesia, these agents prevent tachycardia and hypertension, decrease the incidence of shivering, and reduce VO2 ***(16, 17).*** Given as 50 mcg doses, a dose of up to 150 mcg will suppress postoperative shivering in approximately 905 of cases in less than 5 minutes ***(18).*** Clonidinel, in patients at risk during cardiac over vascular surgery, may provide better haemodynamic control and prevent mycordial ischaemia ***(14, 19).*** In coronary artery disease undergoing vascular surgery morbidity.

مستشفيات بنها الجامعية

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السيد الأستاذ / أمين الجامعة

تحية طيبة وبعد ، ، ، ،

نتشرف بالإفادة بأن مجلس قسم التخدير والعناية المركزة وافق بجلسته رقم ( )

بتاريخ ٥ / ٦ / ٢٠١٦ علي ترشيح السيد الطبيب / اسلام على محمد على شابوب

لدرجة مدرس مساعد بالقسم نظرا لحصوله علي درجة الماجستير من كلية طب بنها في

تخصص تخدير وعناية مركزة دور علما بأنه ملتزم في عمله

ومسلكه خلال عمله في وظيفة معيد بمستشفيات بنها الجامعية .

وتفضلوا بقبول وافر الشكر والاحترام .....

رئيس مجلس الإدارة

(أ.د/ [illegible])