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Neuropharmacological Factors, Biliary Motility and Pancreatitis

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The article by Kwok-Hung Lai [1] obligates us to amplify this issue. For this reason, we will add some additional comments.

Impaired drainage of the pancreatic exocrine secretion is one of the most important pathophysiological factors underlying pancreatic inflammation. Anatomical and/or functional obstacles at the choledocum and the sphincter of Oddi are among the most relevant etiopathogenic factors of this disorder. In this regard, it has been demonstrated that an alpha-adrenergic blockade interferes with gallbladder and biliary tract drainage [2]. This neuropharmacological-induced disorder is similar to the biliary dyskinesia registered in patients showing increased levels of plasma serotonin [3, 4]. Regarding this, it is a very well-known fact that serotonin blocks alpha-adrenergic receptors at both the muscular and the vascular levels [5]. The fact that clonidine, an $alpha_2$ agonist drug which lowers plasma catecholamines, is able to suppress hepatic colic is consistent with the above [6, 7, 8, 9]. This finding fits well with the demonstrated fact that the physiological role of cholecystokinin (CCK) is not observed when plasma catecholamines are elevated [10]. This abnormality is present in all patients affected by pancreatitis and all severe acute and chronic diseases [11, 12, 13, 14, 15, 16].

We agree with Kwok-Hung Lai with respect to the role played by the sphincter of Oddi as an etiopathogenic factor of pancreatitis; however, we believe that this disorder should be resolved using neuropharmacological manipulation means and not by means of a sphincterotomy, which has been included among the factors which can trigger gastrointestinal cancer [17, 18]. Since the early nineties, we have successfully treated all types of inflammatory pancreatic diseases with i.m. clonidine [6, 19, 20]. This $alpha_2$ agonist suppresses pain immediately and provokes normalization of amylase plasma levels within the first hours of its administration. We did not observe any additional hypotension to that noted before clonidine injection and, on the contrary, we usually found an increase in blood pressure. Although we have published some preliminary reports, we found it impossible to carry out any double-blind trials because the acute-pancreatitis patients recovered within the first 2-3 days of clonidine therapy. Furthermore, clinicians do not have the neuroautonomic or neuropharmacological knowledge needed to utilize this therapeutical approach. However, we will now describe the mechanisms involved in this issue. Clonidine immediately suppresses the salivary and pancreatic exocrine secretion. In effect, a single dose of the drug administered to dogs, whose pancreatic excretory ducts had been previously catheterized, was able to suppress pancreatic juice secretion, not only during basal condition but also after the administration of secretin or pancreozymin, two powerful excitatory hormones [12].

In addition to the above, it has been demonstrated that clonidine reduces adrenal sympathetic rather than neural sympathetic activity. This statement is supported by the finding that, although clonidine reduces

plasma adrenaline and noradrenaline, the drug increases the noradrenaline/adrenaline plasma ratio [21, 22, 23]. This fact would explain why clonidine does not reduce but instead increases blood pressure in severely ill (stressed) patients. In order to facilitate the understanding of this phenomenon, it is necessary to know that clonidine acts, almost selectively, on the C1-adrenergic nuclei located at the rostral ventrolateral medullary area, which is responsible for adrenal gland secretion [24]. These nuclei, and not the locus coeruleus (LC) pontine noradrenergic nucleus, are hyperactive in all severely ill (stressed) mammals [23].

The above information indicates that clinicians should be knowledgeable regarding physiology, pharmacology, neurochemistry, and all basic science disciplines.

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