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No More Intravenous Procaine for Pancreatitis Pain?

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Having been trained in the German-speaking world of pancreatology, I was taught that the pain of patients with pancreatitis is special – special in that it responds well to intravenous procaine, a drug then commonly used as either a local anaesthetic or a cure for ventricular arrhythmias. Special also in that drugs generally used for a pain in other diseases were 'verboten' in pancreatitis because they would make the disease worse. Since hands-on experimental work had taught me that pancreatitis is, indeed, a very special disease, I followed the rules for medical residents and pancreatitis patients in pain received their 24-hour infusions of procaine.

First doubts about this approach arose when many patients treated in this way remained in pain, required high doses of additional analgesics, or developed ECG changes. Due to repeated exposure to the Anglo-Saxon world of pancreatology, my belief was further shaken when British or Canadian pancreatitis patients with pain were not regarded as special at all: they received morphine for severe pain just like cardiac or tumour patients, it relieved their symptoms sufficiently well, and it did not seem to negatively affect the course of the disease.

Many years later, when I participated in the steering committee of an international pancreatitis study and suggested to ask in the questionnaire whether patients had been treated for pain with procaine, the response of my peers from Italy, France, Spain, Scandinavia and the UK ranged from bafflement to mild ridicule. None of them had ever heard of procaine as a treatment of pain in acute pancreatitis.

The final results of said study as well as consultation of standard textbooks from the countries of my colleagues made me realise that pain in pancreatitis is special only – and treated with procaine only – in the German-speaking world. Why the rest of the world had failed to see the wisdom of this approach became quickly apparent during a Medline/PubMed search which, at that time, did not result in a single article or case report when 'procaine *and* pancreatitis' were entered as a search item.

Having failed to determine by conventional means the source of this uniquely Germanic approach to treating pancreatitis patients, I started asking more senior colleagues whether they knew about the historic roots of the procaine treatment. It turned out that the first large-scale multicentre trial for acute pancreatitis (the salmon calcitonin trial published in 1979 [1]) contained a mandatory baseline therapy for both arms of the study that, among other items like intravenous nutrition and fluid replacement, included a 24-hour procaine infusion for the treatment of pain. When I asked the principal investigators of the calcitonin trial why they had included procaine in the baseline treatment of the protocol, the answer was a surprise. This approach to pain treatment was also new to them at the time, but one of the centres, who they correctly predicted to contribute a large number of patients to the trial, had insisted on making the procaine infusion a

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requirement in the baseline therapy because that was the standard at their hospital.

During the late 1970s most major centres with an interest in pancreatitis contributed to the calcitonin trial and a multitude of interns and residents (those who usually have to do the paperwork for clinical trials) treated patients with pancreatitis for the first time, and with great enthusiasm, within the framework of a multicentre trial. Since the protocol of this trial included procaine for pain as a mandatory baseline therapy the widespread knowledge about this approach is no longer surprising. When the same recommendations regarding procaine for pancreatitis pain resurfaced in various review articles and textbook chapters it slowly became conventional wisdom and even part of the German guidelines for the treatment of acute pancreatitis [2]. While the calcitonin trial could not demonstrate a significant treatment advantage for the compound under investigation it still had two lasting – and rather unexpected – effects: it established an effective network of clinical centres that continued to perform excellent multicentre pancreatitis trials and it inadvertently made intravenous procaine the standard pain treatment for pancreatitis patients.

The question is why the latter was never questioned, challenged or clinically tested over so many years. The answer has, in my opinion, nothing to do with an aversion to challenging clinical paradigms in the German-speaking world – quite the opposite seems to have happened in recent years – but to a deep-rooted cultural reflex. No society has ostracised, prosecuted or regulated the use of opiates for any purpose, be they recreational or medical, with greater zeal and efficiency over the last two centuries than the Germans.

The bureaucratic hassles nowadays imposed by the authorities on physicians who wish to prescribe opiates for terminally ill cancer patients are only one of many manifestations of this cultural reflex. Only around half of the German general practitioners who care for bedridden patients at home have even applied for a federal license that would permit them to prescribe opiates. Statistically, German cancer patients with a predicted survival of less than 12 months receive only one quarter of the opiates that would be administered to the same patients in Scandinavia, the Netherlands or the UK. The most frequent rationalisation for this fact by German physicians is that the patient could 'become addicted'.

Before this cultural background it may be less surprising that procaine infusions for pain were so readily accepted as a treatment modality for pancreatitis pain. The fact that a cultural icon like Sigmund Freud was instrumental in the discovery of the pain relieving effect of the procaine class of agents might also have helped to delay the clinical evaluation of this treatment. Fortunately, this has happened at last.

In a first trial the effect of procaine on pancreatitis pain was compared to that of opiates and opiates were, not surprisingly, found to be much more effective [3]. The design of this trial, however, could not answer the question whether procaine had any effect on pain at all. The latter question was tested in a study by Kahl et al. [4] published in the present issue of *Digestion* on more than 100 patients with acute pancreatitis. The results are simply devastating. Not only is continuous procaine infusion completely ineffective in reducing pain in patients with acute pancreatitis, but giving a procaine infusion together with opiates 'as needed' – rather than at regular intervals – will result in greater pain for the patient while failing to reduce the total dosage of opiates administered. Even the percentage of patients in which procaine could potentially have reduced the total amount of opiates required for pain relief (14%) is well below the rate that would be expected from a placebo treatment.

Should this make us regard patients with pancreatitis pain no longer special and prompt us to treat them according to WHO guidelines or like the rest of the world? Not so fast. Remember, Winston Churchill using opium in his college days is not an accepted part of our German heritage. While not a single original report in the literature supports the use of procaine for pancreatitis pain, cultural reflexes run deep and old paradigms die hard.

For years to come the reader should therefore expect old pancreatitis hands to argue that procaine inhibits phospholipase A_2 [5] and opiates negatively effect sphincter motility [6]. You could answer them that inhibition of phospholipase A_2 in a test tube may have no relevance to pain *or* pancreatitis whatsoever and that even much more potent broad spectrum protease inhibitors like gabexate have no beneficial effect in pancreatitis at all [7]. You could also add that no study has shown that, once a patient suffers from pancreatitis, sphincter motility would be of any major concern or that an effective pain treatment with opiates has any negative influence on the disease course. Expect them to remain unconvinced.

Ultimately, pain treatment with intravenous procaine will first disappear from German language review articles and textbook chapters as a result of the Magdeburg trial and then, with some delay, from clinical grand rounds. But you can count on our German cultural reflexes to quickly come up with another treatment modality that allows us to withhold the opiates from our patients in

pain. For pancreatitis patients the alternative may turn out to be thoracic epidural analgesia (another German invention [8]) that has an added benefit in its effect on bowel paralysis. Although the administration of thoracic epidural analgesia requires considerable technical expertise and only a minority of patients may qualify because of its inherent complications, you can expect its widest usage in the German-speaking world because it allows our instincts to avoid the opiates.

The art of medicine is, after all, based only in part on science and the rest is governed by emotions. The science for treating patients with pancreatitis pain with opiates has finally arrived – let's see how well we will deal with our emotions and cultural reflexes.

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