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Metamizole is not as Safe as We Think or Assume

Metamizol Düşündüğümüz Kadar Güvenli Bir İlaç Değil

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I have read the article by Uzun et al with great interest (Turkish Neurosurgery 20:341-347, 2010). The authors have designed a double-blind randomized clinical research with 63 patients undergoing surgery for lumbar disc disease. The patients were allocated into 3 groups. Group I patients received 1 gm of intravenous paracetamol and 1 gm of intravenous metamizole at the end of the operation whereas patients in Group II received only 1 gm of paracetamol at the end of the operation. Group III was the placebo group and did not receive paracetamol or metamizole. All three groups of patients were also given morphine through patient controlled analgesia (PCA) pumps. All patients were evaluated in terms of pain (evaluated using the Numeric Pain Rating Scale [0-3]), morphine consumption and patient satisfaction at post-operative 15 and 30 minutes and 1st, 2nd, 6th and 24th hours. The graphs depicting morphine consumption showed that Group III patients consumed more than those who were given paracetamol plus metamizole or paracetamol alone. The authors concluded that addition of metamizole to paracetamol along with morphine PCA offered an advantage over single morphine PCA and paracetamol with respect to early postoperative pain treatment and patient satisfaction.

There are two things that disturb me about this study. First is the unequal use of morphine among all patients (...In Group C, one patient's morphine demand was 941 and two patients' demand was 398, causing an extreme increase in the total number of demands...). If only all patients were given a higher bolus and maintenance dose of morphine as the baseline pain medication, the visual pain scale scores and the conclusions derived from them would have been scientifically comparable. When you let the patient use unlimited PCA then not only the groups but also each individual in the research become heterogeneous in terms of pain medication within the bloodstream and finally we end up with 63 different groups with one patient in each.

My second concern is about the use (and later suggestion) of metamizole not only in this experiment but also all around Turkey. Metamizole is a historic drug first synthesized in 1920 by the German company Hoechst AG. Its mass production started in 1922. It remained freely available worldwide until the 1970s, when it was discovered that the drug carried a risk of causing agranulocytosis - a potentially fatal condition. Metamizole was banned in Sweden in 1974, and in the United States in 1977. Since then, more than 30 countries (including Japan, Australia, Iran, and several of the European Union member nations) have followed suit. In these countries, metamizole is only occasionally used as a veterinary drug. In some EU countries like Germany, Hungary, Italy, Portugal and Spain it is a prescription drug. In other parts of the world (including Bulgaria, Mexico, India, Egypt, Brazil, Poland, Russia, Turkey, Macedonia, Romania, Israel, and some developing countries) metamizole is still freely available over-the-counter, and remains one of the most popular analgesics.

I myself have not prescribed or used metamizole for the last 18 years but four years ago I had witnessed a serious incident where a severe head injury patient that I operated upon was given metamizole during the night by a junior doctor on-duty. The patient developed severe agranulocytosis in the following days with absolute count of neutrophils as low as 55 per cubic mm (WBC 2900 x 1.9% neutrophils). We had to isolate the patient first. After further decrease with no increase in neutrophil count we did perform a bone marrow aspiration. Microscopy of the aspirate showed normal maturation in erythroid and megaloblastic series whereas there was a pause in maturation in the myeloid series at the promyelocyte stage. G-CSF (granulocyte colony-stimulating factor [Neupogen, Roche] had to be given daily and was given as 10 million units subcutaneously for 4 consecutive days. Ceftazidime 6 gm IV and flucanozole 200 mg IV were added as protection. The neutrophil count exceeded 1000 two days after initiation of G-CSF treatment and returned to normal in a week. The patient finally recovered from the situation but it was a hectic and unpleasant plus costly experience.

Drs Uzun et al suggest the use of metamizole stating that "... the incidence of this side effect (agranulocytosis) is a matter of debate and may be dependent on genetic factors, and the real incidence of agranulocytosis due to metamizole is not known". Actually there is fresh contrary data from Sweden that shows that the risk is there and is more real than we all probably think of it. Interestingly enough Sweden, the first country in the world to ban metamizole, lifted the ban in 1995 and then re-introduced it in 1999. Considering the high standard of Swedish medicine and a defined period as such, there could not be a better time to re-evaluate the exact risk of metamizole. Such a publication came from Umea (Northern Sweden) in 2002. Bäckström et al stated that there were 10 cases of agranulocytosis submitted to the Swedish Adverse Drug Reactions Advisory Committee between 1996 and 1999 (1). Given certain assumptions including the actual amounts prescribed, the risks of agranulocytosis during metamizole treatment was given as approximately one out of every 31,000 metamizole-treated inpatients and one of every 1400 metamizole-treated outpatients.

In conclusion I think there are enough reasons not to use metamizole at all in medical practice. I do not wish anybody an experience like mine before reaching such a decision.

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