Reviewer’s report

Title: The effects of ibuprofen on the physiology and survival on the rabbit endotoxic shock

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Reviewer: Prof Jean-Louis Vincent

Level of interest: A paper of limited interest

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

The authors studied the effects of ibuprofen administration on basic physiologic variables, hematologic variables, blood thromboxane concentrations and urine prostaglandin E2 concentrations during endotoxic shock in rabbits. Ibuprofen administration reduced the degree of arterial hypotension and prolonged survival.

General comments:
Why the authors conducted this study is unclear. There have been many studies evaluating the effects of ibuprofen in various models of septic shock and this model of endotoxic shock in the rabbit does not seem to be peculiar in any way. Furthermore the effects of ibuprofen have been studied already in humans with septic shock. The manuscript does not describe this literature but I can try to help. The first major study of ibuprofen in endotoxic shock was performed by Jacobs et al (J Clin Invest 70: 536, 1982). This study indicated that ibuprofen can limit the degree of hypotension, acidosis and decrease in cardiac index in endotoxic shock. In a hyperdynamic sepsis model in dogs Fink et al (Ann Surg 200: 619, 1984) reported ibuprofen (like indomethacin) restored the normal hemodynamic pattern. Balk et al (Crit Care Med, 16: 1128, 1988) studied the dose response to ibuprofen in endotoxic shock in dogs. Again there was a significant effect on arterial pressure. However, Hulton et al (Surgery 98: 291, 1985) reported no major metabolic effect in E. coli sepsis in dogs. They even raised the possibility of a deleterious renal effect of ibuprofen. Nevertheless, the same group of investigators (Revhaug et al, Arch Surg 123: 162, 1988) demonstrated that ibuprofen could significantly reduce the signs of sepsis in volunteers receiving a small dose of endotoxin. Gnidec et al (J Appl Physiol 65: 1024, 1988) showed that ibuprofen administration in a peritonitis model in sheep could limit the increase in edema. Nishijima et al (Am J Physiol 255: 177, 1988) also studied the effects of ibuprofen on regional blood flow during porcine endotoxic shock. Following this, Metz and Sheagren published a comprehensive paper on the effects of ibuprofen in animal models of septic shock (J Crit Care 5: 206, 1990). Ertel et al (J Surg Res 53: 55, 1992) showed that ibuprofen administration could also restore cellular
immunity and decrease susceptibility to sepsis following hemorrhage in mice. Coran et al (J Surg Res 53: 272, 1992) showed that the administration of ibuprofen in septic shock in dogs did not reduce cytokine levels, suggesting that ibuprofen exerts its effect at a more distal side of the mediator response. Fletcher et al (Ann Surg 217: 686, 1993) showed that ibuprofen administration could dramatically reduce TNF-induced mortality. Herbertson et al showed that ibuprofen administration in endotoxic shock in pigs could prevent the early hemodynamic changes following endotoxemia but not the later changes (Crit Care Med 21: S135, 1993). Winslow and Dorinsky showed that ibuprofen had few direct effects on regional blood flow distribution after endotoxin administration (J Crit Care 9: 159, 1994).

Other investigators (Sigurdsson and Youssef, Acta Anesthesiol Scand 38:33, 1994) also studied the effects of ketoprofen in endotoxic shock in sheep and also showed that this related agent ameliorated the cardiorespiratory alterations induced by endotoxin. There may also be important differences between endotoxic shock models and peritonitis models (see Reddy et al, Am J Physiol 281: L537, 2001).

The authors should also refer more extensively to the clinical studies by Haupt et al and especially Bernard et al in patients with severe sepsis.

In view of all these studies, the reader wonders why the investigators conducted the present experimental study that seems to add very little to the present knowledge.

Specific comments:
1. Abstract: Why do the authors refer to the undesirable effects of endotoxic shock on respiratory rate and heart rate? Is it not a normal response to develop tachypnea, tachycardia and fever when endotoxin is administered?
2. End of abstract and elsewhere in the text: Patients may not develop endotoxic shock but septic shock in a broader sense.
3. Introduction: The introduction should be extended in view of this literature review and raise important questions which were not addressed in the previous studies.
4. Results: The entire results section is difficult to read. It seems that ibuprofen administration had hardly any effect on respiratory rate and heart rate (but this is of minor importance).
5. Discussion, third paragraph: Reference to the work by Bernard et al is confusing here: Bernard did clinical studies with ibuprofen.
6. Discussion: Once again, the restoration of vascular tone resulting in a greater arterial pressure may be beneficial but the effects on heart rate and respiratory rate are more questionable.
7. Discussion: Again, the authors should largely refer to the clinical study performed by Bernard et al: Is it still necessary to perform these animal experiments when the effects in humans have been well described?
8. Discussion: Many studies have shown that endotoxin administration can result in an acute decrease in the white blood cell count. Can the authors propose an explanation to explain the lack of effect of ibuprofen on white blood cell count and platelet count?
9. The effects of ibuprofen on arterial pressure are worth a figure.
10. Figure 1: Why does the respiratory rate go down to zero only in group 2?

Competing interests:

None declared.