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Phase 1 safety and pharmacokinetic study on the use of pioglitazone in critically ill patients with sepsis: A Randomized Clinical Trial

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Dear Editor,

Sepsis is a significant clinical problem and contributes to morbidity, mortality and higher healthcare costs [1, 2]. Besides appropriate and timely antibiotic administration there are few therapies that show benefit in sepsis clinical trials. One possible explanation is the lack of available pharmacokinetic (PK) data, especially as it relates to children.

The thiazolidinediones (TZDs), pioglitazone and rosiglitazone, are Food and Drug Administration (FDA)-approved compounds that activate peroxisome proliferator-activated receptor-gamma (PPAR γ). Preclinical studies from our laboratory demonstrate that treatment with PPAR γ ligands reduces inflammation and improves survival [3] and that PPAR γ expression is decreased in peripheral blood mononuclear cells of children with septic shock compared with controls [4].

Septic patients admitted to the PICU with a weight between 30–90 kg were considered eligible for the study and approached for consent. Subjects were randomized to pioglitazone

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treatment or usual care (control group). Participants randomized to the treatment group received pioglitazone hydrochloride (0.5 mg/kg/dose) every 24h (± 3) for five days.

We enrolled 12 patients with severe sepsis or septic shock in the study (Supplement Figure 1). Eight patients were randomized to receive pioglitazone and four patients received usual care (control). The demographic and clinical outcomes are demonstrated in Supplement Table 1. Baseline characteristics were similar between groups.

The PK profiles for the eight subjects randomized to the pioglitazone group are illustrated in Figure 1. Because of the low concentration levels in some pioglitazone subjects we investigated whether the route of administration affected pioglitazone levels. The AUC estimates were higher for subjects who took pioglitazone by mouth (PO), and similar to those found in adolescents with type 2 diabetes [5], compared to subjects who took pioglitazone by NG tube [median 5,162 ng*h/ml (IQR 3,114–8,270) vs. 1,579 (IQR 335–4,020) respectively, $p=0.08$] (Figure 1 c&d). Concentration differences between PO and NG groups in our study are unknown and could be related to adherence to the tube, gastroparesis and delayed gastric emptying or gastric pH.

During the study a total of 12 serious adverse events occurred but none were related to the study drug. The total number of non-serious adverse events were 76 but only three events were considered possibly related to the study medication. One subject developed a maculopapular rash and two subjects developed increased lipase.

Excluding the subject who required ECMO support, we examined the effect of pioglitazone AUC on inflammatory markers and found a high inverse correlation between inflammatory markers and pioglitazone AUC ($p=0.003$). Individual inflammatory markers were plotted against study day. Age and gender effects were first tested for the selected biomarkers and found not significant. The resulting linear regression coefficients and their significance levels are summarized in Supplement Table 2. We found that the AUC of pioglitazone was significantly associated with a reduction in IL-6, IL-8, resistin and TNF- α .

This is the first study, to our knowledge, to study pioglitazone as a potential sepsis therapy during critical illness. We demonstrate that pioglitazone is safe when administered to critically ill pediatric patients. Furthermore, pioglitazone exposure was associated with a reduction in inflammatory mediators.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HW and the institution, CCHMC, hold patents for sepsis-related biomarkers.

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References

1. Schlapbach LJ, MacLaren G, Festa M, Alexander J, Erickson S, Beca J, Slater A, Schibler A, Pilcher D, Millar J, Straney L, Australian, New Zealand Intensive Care Society Centre for O, Resource E, Australian, New Zealand Intensive Care Society Paediatric Study G, (2017) Prediction of pediatric sepsis mortality within 1 h of intensive care admission. *Intensive Care Med* 43: 1085–1096. [PubMed: 28220227]
2. Thompson K, Taylor C, Jan S, Li Q, Hammond N, Myburgh J, Saxena M, Venkatesh B, Finfer S, (2018) Health-related outcomes of critically ill patients with and without sepsis. *Intensive Care Med* 44: 1249–1257. [PubMed: 29951846]
3. Kaplan JM, Cook JA, Hake PW, O'Connor M, Burroughs TJ, Zingarelli B, (2005) 15-Deoxy-delta(12,14)-prostaglandin J(2) (15D-PGJ(2)), a peroxisome proliferator activated receptor gamma ligand, reduces tissue leukosequestration and mortality in endotoxic shock. *Shock* 24: 59–65. [PubMed: 15988322]
4. Kaplan JM, Denenberg A, Monaco M, Nowell M, Wong H, Zingarelli B, (2010) Changes in peroxisome proliferator-activated receptor-gamma activity in children with septic shock. *Intensive Care Med* 36: 123–130. [PubMed: 19760394]
5. Christensen ML, Meibohm B, Capparelli EV, Velasquez-Mieyer P, Burghen GA, Tamborlane WV, (2005) Single- and multiple-dose pharmacokinetics of pioglitazone in adolescents with type 2 diabetes. *J Clin Pharmacol* 45: 1137–1144. [PubMed: 16172178]

Fig. 1.

(A) Treatment group and route for pioglitazone administration by subject. (B) Pharmacokinetic profile for subjects randomized to the pioglitazone group. Pioglitazone concentration of individual subjects over time. Black symbols = subjects who received drug by mouth (PO route). White symbols = subjects who received drug by NG route. (C) Pioglitazone area under the curve (AUC) estimates for subjects by route of administration. Black symbols = PO route, White symbols = NG route. (D) Pioglitazone concentration as the total AUC/number of days receiving the drug in subjects who took the drug PO versus by NG tube.