change in opiate use is unsophisticated at best" and that "IV acetaminophen is a tool like any other in our armamentarium. If we use a tool ineffectively, then we are the problem—not the tool," and we reiterate our call for the identification of patient subgroups and IV acetaminophen administration schedules most likely to result in benefit.[1] However, in all fairness and to stay true to generally accepted scientific principles, one has to consider the possibility that no benefit may be found at all.

Riou *et al.* stated three main limitations: (1) the validity of opioid utilization from billing data, (2) heterogeneity in treatment groups based on acetaminophen doses administered, and (3) residual confounding. We agree with all three and have specifically highlighted the first in our manuscript. However, any bias attributable to mismatch between billing for opioids and administered opioids should be independent of IV acetaminophen use and thus would minimally affect our findings. Further, it is more likely that billing for opioids occurs when dispensed by the pharmacy and not when prescribed, thus increasing the correlation between billing and administration. Heterogeneity in treatments is unavoidable in studies using real-world data and actually demonstrates the value of such data over clinical trials. Here, various treatment regimens or protocols may be used, whereas trials often focus on a standard that is not generalizable as discussed above. Residual confounding will always remain when using observational data; the goal of sensitivity analyses is not to eliminate this (which would be impossible given the data used) but rather to demonstrate robustness of results using various approaches. Although we appreciate the authors' suggestion to apply a propensity score analysis or "another sophisticated multivariable matching process," given the number of treatment groups under study this would not be possible because the situation under study is more complicated than just comparing patients who received IV acetaminophen with those who did not. In our study we identified nine treatment groups based on dose of IV acetaminophen used (0, 1, or more than 1 dose) and day of use (day of surgery, postoperative day 1, postoperative day 2, or later). This was represented using three separate variables, because overlap between these groups exists. Rather than considering this a limitation, we feel that this information is valuable in that it shows the current dosing regimens in use. Resorting to an approach where just one dosing scheme would be compared with no use would entail the same limitations regarding generalizability. Thus, we respectfully disagree with Riou *et al.* that "the amount of new information is relatively limited," because our study shows real-world utilization of IV acetaminophen in a distinct surgical cohort likely to include patients who may benefit from this drug (*i.e.*, those who cannot tolerate oral medication). We found IV acetaminophen to be mostly used as a single-dose administration on the day of surgery; this does not coincide with use in trials such as the one referred to by Riou *et al.*, where the treatment regimen under study was "propacetamol 2 g every 6 h."[4]

In summary, we appreciate the comments put forward by Dr. Steadman and Riou *et al.*, because these comments are helpful to understand the results from our study in their proper context of real-world use of IV acetaminophen that revealed no benefit and possibly less than effective administration regimens.

Competing Interests

The authors declare no competing interests.

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References

1. Wasserman I, Poeran J, Zubizarreta N, Babby J, Serban S, Goldberg AT, Greenstein AJ, Memtsoudis SG, Mazumdar M, Leibowitz AB: Impact of intravenous acetaminophen on perioperative opioid utilization and outcomes in open colectomies: A claims database analysis. Anesthesiology 2018; 129:77–88
2. Martinez V, Beloeil H, Marret E, Fletcher D, Ravaud P, Trinquart L: Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth 2017; 118:22–31
3. Ilfeld BM, Gabriel RA, Eisenach JC: Liposomal bupivacaine infiltration for knee arthroplasty: Significant analgesic benefits or just a bunch of fat? Anesthesiology 2018; 129:623–6
4. Aubrun F, Kalfon F, Mottet P, Bellanger A, Langeron O, Coriat P, Riou B: Adjunctive analgesia with intravenous propacetamol does not reduce morphine-related adverse effects. Br J Anaesth 2003; 90:314–9

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Experimental Controls in Lipid Resuscitation Therapy

To the Editor:

We read with interest the recently published work by Umar *et al.*[1] The authors assert that antagonism of free-fatty acid receptor G-protein-coupled Receptor 40 (GPR40) with a G-protein-coupled receptor small

molecule inhibitor (GW1100) blocks all cardioprotective effects of lipid emulsion in animal models of ischemia-reperfusion and bupivacaine-induced cardiotoxicity. The hypothesis is appealing given that a fat-based antidote could logically work by interacting with fatty-acid receptors. We believe, however, that the study lacks appropriate controls and relies on untested assumptions to justify its conclusions.

First, the role of GPR40 in cardiac tissue is unclear. Itoh *et al.* identified GPR40 as a channel in the gastrointestinal-tract that modulates insulin secretion from the pancreas in response to stimulation with free-fatty acids.[2] The current work is the first to identify GPR40 in cardiac tissue but fails to identify its physiologic role in normal cardiac function. Given that insulin signaling modulates bupivacaine toxicity,[3–5] and that GPR40 inhibition will abolish insulin-release from the pancreas, appropriate controls for insulin and glucose levels would strengthen the argument for a cardiac (instead of pancreatic) effect. Alternatively, the authors could use a cardiac-specific knockout to confirm a cardiac specific effect.

Second, the authors use GW1100, a small molecule antagonist of GPR40 without a clear understanding of the cardiac side effects of inhibiting it. Other, off-target effects of GW1100 (*e.g.*, pancreatic G-protein coupled receptor 120) are known and without characterizing its pharmacokinetics at the doses used, it is possible that it perturbed pancreatic calcium homeostasis and insulin release.[6] Experiments with other GPR40 antagonists (*e.g.*, DC260126[7]) could confirm a GPR40-based effect, but as presented the results are not specific for GPR40.

The paper lacks positive controls to test whether the combination of GW1100 and ischemia (or bupivacaine) is an unrecoverable insult. The authors used a predosing control of GW1100, which showed physiologic effects of GW1100. Other physiologically relevant drugs (including insulin and the protein kinase B inhibitor Wortmannin) exert combinatorial toxicity.[2,4] Given that such an interaction between GW1100 and ischemia-reperfusion injury and/or bupivacaine toxicity could explain their results, the lack of positive controls (*e.g.*, a titratable and recoverable insult) is puzzling.

The authors' data are impressive, but the results are not specific for cardiac effects mediated by GPR40 or lipid emulsion. For example, replacing GW1100 with concentrated potassium chloride would produce a near-identical set of data. Evidence from several laboratories indicates that multiple properties (*e.g.*, volume expansion, accelerated redistribution, positive inotropy, and attenuation of ischemia-reperfusion injury) drive the benefit lipid resuscitation therapy.[8] The authors do not address how their results would comport with these other theories or use controls to obviate the other effects (*e.g.*, How would GW1100 alter volume or redistribution effects?). Given these concerns, the simplest explanation of the findings by Umar *et al.* is that the combination of GW1100 and ischemia or bupivacaine causes cardiotoxicity that has no bearing on the function of lipid emulsion.

Competing Interests

Dr. Weinberg is an officer, shareholder, and paid consultant of ResQ Pharma, Inc., Chicago, Illinois.

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References

1. Umar S, Li J, Hannabass K, Vaillancourt M, Cunningham CM, Moazeni S, Mahajan A, Eghbali M: Free fatty acid receptor G-protein-coupled Receptor 40 mediates lipid emulsion-induced cardioprotection. Anesthesiology 2018; 129:154–62
2. Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y, Uejima H, Tanaka H, Maruyama M, Satoh R, Okubo S, Kizawa H, Komatsu H, Matsumura F, Noguchi Y, Shinohara T, Hinuma S, Fujisawa Y FM: Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. Nat Med 2003; 422(6928):2001–4
3. Fettiplace MR, Kowal K, Ripper R, Young A, Lis K, Rubinstein I, Bonini M, Minshall R, Weinberg G: Insulin signaling in bupivacaine-induced cardiac toxicity: Sensitization during recovery and potentiation by lipid emulsion. Anesthesiology 2016; 124:428–42
4. Stehr SN, Pexa A, Hannack S, Heintz A, Heller AR, Deussen A, Koch T, Hübler M: Insulin effects on myocardial function and bioenergetics in L-bupivacaine toxicity in the isolated rat heart. Eur J Anaesthesiol 2007; 24:340–6
5. Kim JT, Jung CW, Lee KH: The effect of insulin on the resuscitation of bupivacaine-induced severe cardiovascular toxicity in dogs. Anesth Analg 2004; 99:728–33
6. Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, Sugimoto Y, Miyazaki S, Tsujimoto G: Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. Nat Med 2005; 11:90–4
7. Sun P, Wang T, Zhou Y, Liu H, Jiang H, Zhu W, Wang H: DC260126: A small-molecule antagonist of GPR40 that protects against pancreatic β-cells dysfunction in db/db mice. PLoS One 2013; 8:1–8
8. Fettiplace MR, Weinberg G: The mechanisms underlying lipid resuscitation therapy. Reg Anesth Pain Med 2018; 43:138–49

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