

Local anesthetic associated death: An FDA Adverse Event Screen

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INTRODUCTION

Local anesthetic systemic toxicity (LAST) is a rare but serious complication of local anesthetic use with reports from the past 100 years^{1,2} identifying the potential risk of death associated with LAST. Quantifying and qualifying the risk is challenging due to the rarity and iatrogenic nature of this complication. One tool to investigate drug complications is the FDA adverse events reporting (FAER) database.

METHODS

This study was exempted from review from University of Illinois Chicago institutional review board as it qualified as non-human subject research (STUDY2023-1546). The FAERS database was queried on December 10th 2023 for five commonly used local anesthetics in practice: (lidocaine, bupivacaine, ropivacaine, mepivacaine and chloroprocaine). Records were included if the side effect was “serious”, reported by a “healthcare professional” and “died” was an outcome. Items were further screened if the drug of interest (common name or trade name) was included as the “Suspect Product Names” or named in the “Suspect Product Active Ingredient” column in isolation, another local anesthetic or combined with epinephrine. Secondary analysis was performed by splitting bupivacaine into liposomal bupivacaine and plain bupivacaine. For temporal analysis, events from the past ten years (2014 – 2023) were analyzed and compared to events reported prior to 2014 using Fisher exact test. Frequent “reason for use” and “reactions” were tabulated along with age and gender.

RESULTS

Following screened, 801 reports of death were identified including 427 lidocaine, 215 bupivacaine, 82 ropivacaine, 40 mepivacaine, zero chloroprocaine and 29 mixed that exhibited temporal consistency before and after 2014 (Figure 1). There were 291 male, 327 female and 183 “not specified” in gender. The average age was 46 (median, range 0 – 94) when excluding the 226 “not specified” in the age category. While not represented prior to 2014, after 2014, liposomal bupivacaine was included in 47 reports of death, the same number of reports of plain bupivacaine (Figure 2, fisher-exact test p<0.0001). Excluding blank and “unknown” the most frequent “reason for use” included 218 “anaesthesia”/“anaesthetic”, 84 “pain”, 64 “block” and 44 “analgesia”/“analgesic”. A variety of reactions were reported with cardiovascular reactions reported most frequently (Table 1).



Lidocaine is the most frequently reported cause of death from local

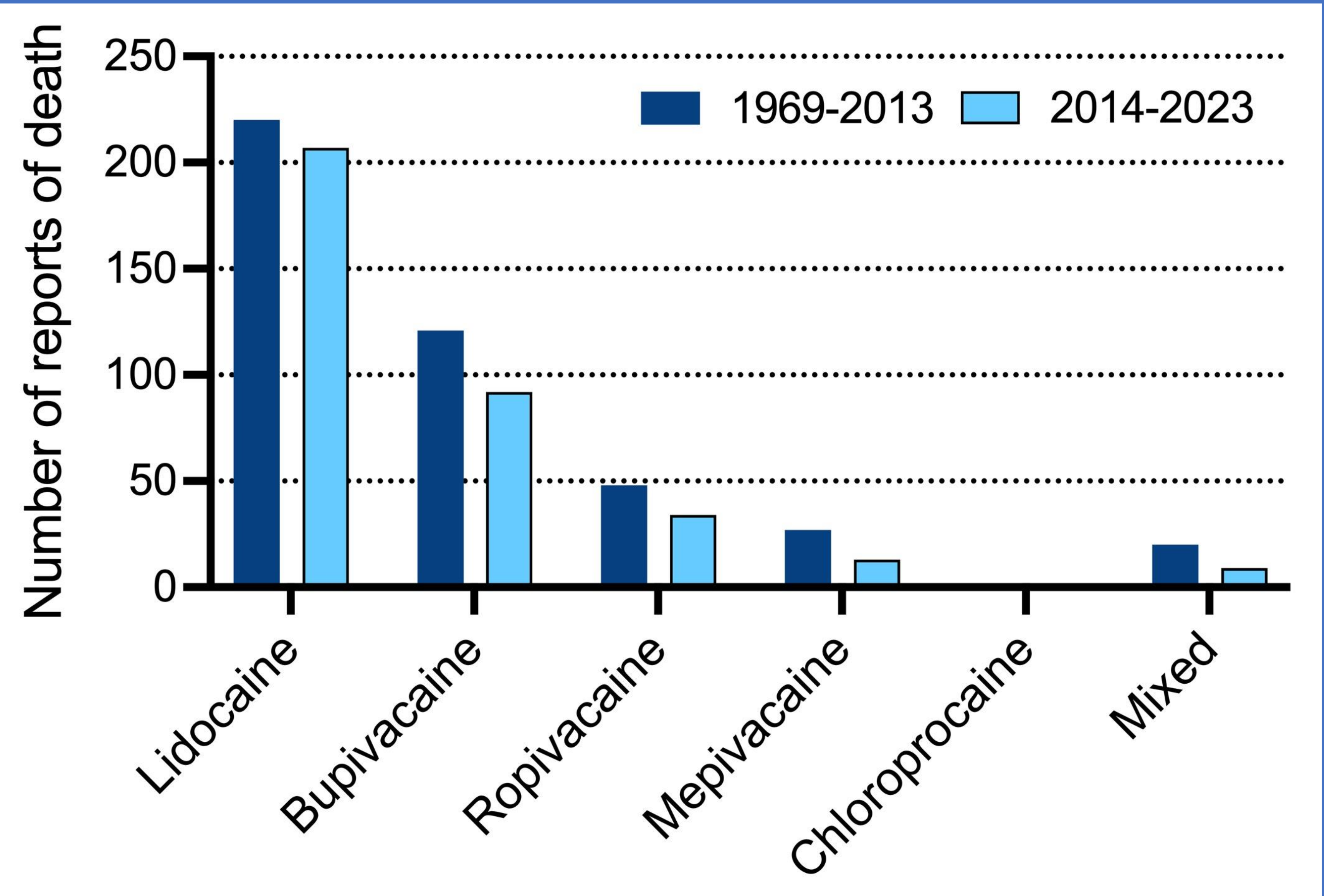


Figure 1: Number of reports of death by local anesthetic prior to 2014 (1969-2013) and within the last 10 years (2014-2023).

Liposomal bupivacaine is reported as frequently as plain bupivacaine, in the setting of rigorous reporting from the manufacturer

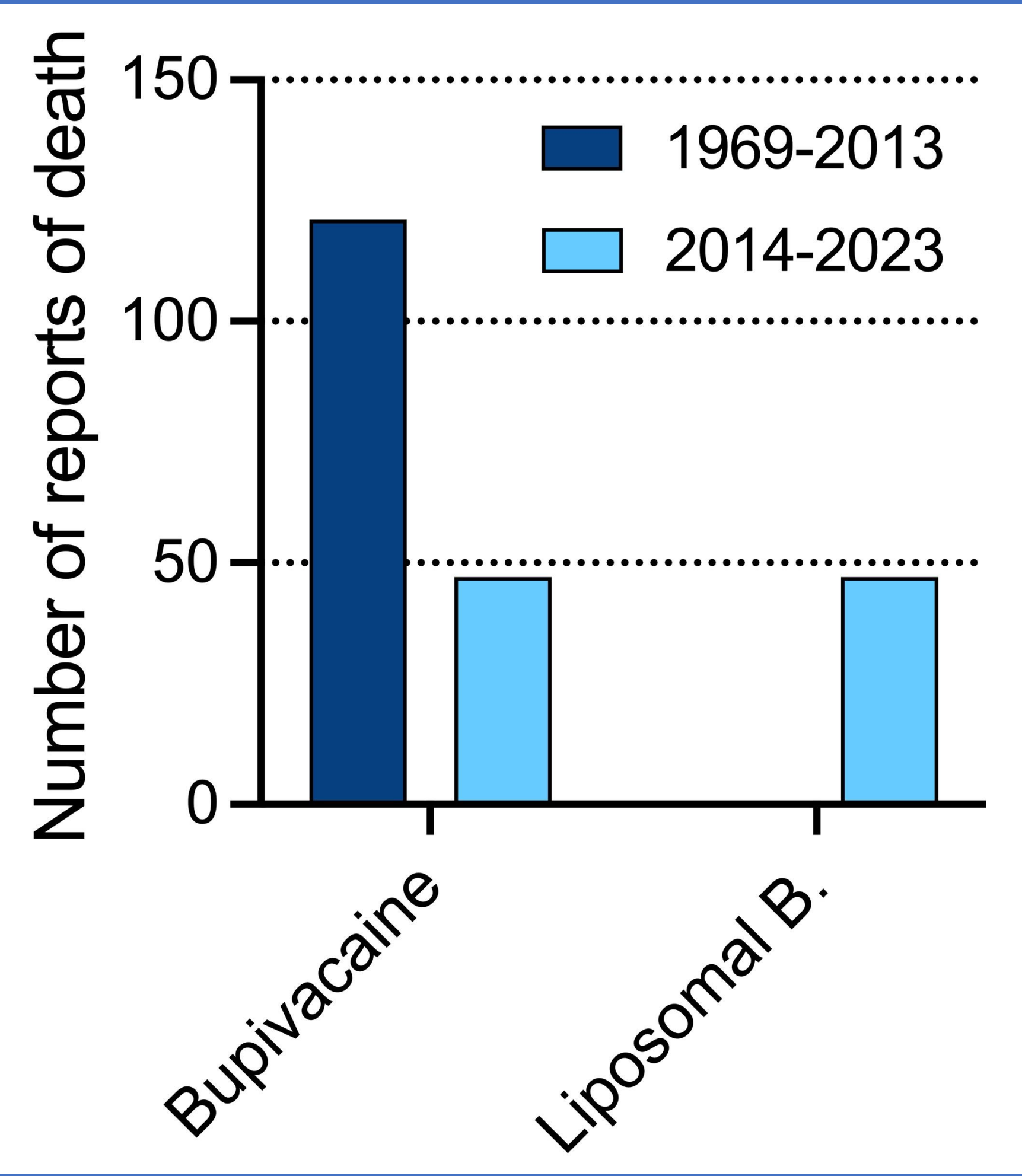


Figure 2: Number of reports of death from bupivacaine divided into liposomal and non-liposomal formulation prior to 2014 (1969-2013) and within the last 10 years (2014-2023).



Figure 1: Reactions from the medication with associated number of reports

Category	Term					
General	Toxicity	Death	Over-dose	Error	ADR	-
	172	252	82	48	12	-
Cardio-vascular	Cardiac-	Hypo-tension	Brady-	Shock	Tachy-	Arrhyth-
	233	67	61	60	56	35
Neuro-logical	Seizure	Brain	Coma	Cereb-	-	-
	144	41	28	26	-	-
Lung-related	Resp-iratory	Pulm-onary	Hypox-	Apnoea	-	-
	111	43	38	20	-	-

CONCLUSIONS

Overall, death from local anesthetic (excluding other medications) was infrequent with 801 reports. Lidocaine was the most frequently reported local anesthetic of the five queried. Despite assertions of safety of liposomal bupivacaine compared with other forms of bupivacaine,³ it was reported as frequently as plain bupivacaine since 2014. There are many limitations to the FAERS database including overreporting (with multiple reports of the same case in some instances) and underreporting (with lack of all cases being submitted). Queries of the database do not provide causality since the cases reported miss other contributing factors including underlying disease of the specific patients. However, it provides one tool to understand adverse reactions to medications, including local anesthetics. The data comports with other sources including case reports and pharmco-vigilance studies that indicate an escalating risk of LAST from lidocaine⁴ and liposomal bupivacaine.⁵ Further guidance to the community about the risk of these agents would benefit patient safety.

REFERENCES

1. Albright G: Anesthesiology 1979; 51:285–7
2. Mayer E: JAMA 1924; 82:876–85
3. PACIRA Biosciences: Non-opioid EXPAREL has a proven safety record at <<https://www.exparel.com/hcp/about-exparel/safety>>
4. Gitman M, Barrington MJ: Reg Anesth Pain Med 2018; 43:124–30
5. Aggarwal N: Expert Opin Drug Saf 2018; 17:581–7