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Effect of Co-Administration of Lidocaine on the Pain and Pharmacokinetics of Intramuscular Amikacin in Children with Multidrug-Resistant Tuberculosis: A Randomized Crossover Trial

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Abstract

Background—Currently recommended treatment for multidrug-resistant (MDR) tuberculosis (TB) includes 4–8 months of an injectable medication, which is poorly tolerated. We evaluated the impact of co-administering lidocaine on pain and pharmacokinetics of intramuscular injections of amikacin in children with MDR-TB.

Methods—Children 8–18 years of age, receiving amikacin for MDR-TB treatment in Cape Town, South Africa, were eligible for this randomized crossover trial. Participants received a 15 mg/kg dose of intramuscular amikacin with and without additional lidocaine (0.2–0.4 mg/kg) on different days, and were randomized to the order of the treatments (the sequence). Participants and staff completing evaluations were blinded to sequence. Samples were drawn pre-dose, and at 1, 2, 4, 6 and 8 hours post-dose for measurement of plasma amikacin concentrations. Pain was assessed by participants using the Wong Baker FACES pain scale (0 to 5) pre-dose, immediately after the injection and then at 30 and 60 minutes. Pharmacokinetic measures were calculated using noncompartmental analysis.

Results—Twelve children were included, median age 11.5 years (IQR 9.9–13.4y). Participant-reported pain scores immediately after the amikacin injection were lower when lidocaine was co-administered: 1.0 (IQR 0.5–2.0) with lidocaine vs. 2.5 (1.0–4.0) without lidocaine ($p=0.004$). The median area under the concentration time curve (AUC_{0-8}) and median maximum plasma concentration (C_{max}) of amikacin were 109.0 $\mu\text{g}\cdot\text{h/mL}$ (IQR 84.7–121.3) and 36.7 $\mu\text{g/mL}$ (IQR 34.1–40.5) with lidocaine compared to 103.3 $\mu\text{g}\cdot\text{h/mL}$ (IQR 81.7–135.0; $p=0.814$) and 34.1 $\mu\text{g/mL}$ (IQR 35.6–46.4; $p=0.638$) without lidocaine, respectively.

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Conclusions—The co-administration of lidocaine resulted in reduced pain immediately after the injection and did not alter amikacin AUC or C_{max} .

Keywords

multidrug-resistant tuberculosis; injectable; lidocaine; amikacin; children

INTRODUCTION

Treatment outcomes for children with multidrug-resistant (MDR) tuberculosis (TB), defined as resistance to at least both isoniazid and rifampicin, are good, with more than 80% of children successfully treated (1). However, current MDR-TB treatment regimens are long, requiring 9 to 18 months of treatment, are poorly tolerated, and are associated with frequent and important adverse effects (2). The second-line injectable antituberculosis drugs, including amikacin, kanamycin, and capreomycin, have been considered a key component of MDR-TB treatment, with guidelines recommending 4–8 months of an injectable agent (3–5). However their use can result in nephrotoxicity, electrolyte abnormalities, and is associated with a risk of permanent sensorineural hearing loss, in up to 25% of children (6). Recent guidance from the World Health Organization (WHO) opened the possibility of limiting injectable use in children with less severe TB. However the newly recommended 9–12 month shortened regimen for MDR-TB includes injectables for at least 4 months, indicating that they will likely remain in use for the near future (5).

In addition to the substantial risk of adverse effects with long-term injectable treatment, their use is complicated by the requirement for parenteral administration. Long-term indwelling catheters, such as portacaths or peripherally inserted central-venous catheters are not feasible in most settings with a high burden of MDR-TB. With constrained health care resources, the risk of catheter infection is problematic, and access to rapid, effective treatment of such infections limited. Hence, the vast majority of children with MDR-TB receive these agents as daily intramuscular injections. The injections are painful for adults and children, and have been cited as one of the worst aspects of MDR-TB treatment (7). They are a source of substantial distress for children, their parents and caregivers, as well as for health care workers who are tasked with delivering this painful intervention for months. Strategies to reduce this injection pain and improve the tolerability of the injectables are urgently needed.

Lidocaine, also known as lignocaine, is a local anesthetic agent, which blocks nerve conduction, producing rapid local anesthesia lasting 1–3 hours, with a maximum effect within minutes (8). Adverse effects are generally mild. However serious systemic adverse effects may rarely occur if there is inadvertent intravascular injection, including central nervous system effects (paraesthesias, visual disturbance, seizures) and cardiovascular effects (hypotension, bradycardia, arrhythmia, cardiovascular collapse) (8). When co-administered with intramuscular injections of ceftriaxone (9, 10) and penicillin (11) lidocaine reduced injection pain without affecting the antibiotics' pharmacokinetics. However this strategy has not been evaluated with the second-line injectable antituberculosis medications. The injectables are rapidly absorbed after intramuscular injection and are renally eliminated unchanged (12, 13). Compared to intravenous injection, there may be

increased variability in the rate and degree of absorption of intramuscularly injected aminoglycosides (14). The impact of lidocaine on the pharmacokinetics of the injectables needs to be considered, as these injectable medications have concentration-dependent activity against *Mycobacterium tuberculosis*, with the maximum plasma concentration most closely associated with efficacy (15). Ototoxicity is associated with cumulative drug exposure (16).

The objective of this study was to evaluate the impact of co-administering lidocaine on the pain and pharmacokinetics of intramuscular injections of amikacin in children and adolescents routinely treated for MDR-TB.

MATERIALS AND METHODS

Trial design

This was a randomized double-blinded two-period crossover trial.

Participants

Children were eligible to the study if they were 8 to 18 years of age, routinely treated for MDR-TB with a regimen including amikacin, and had received amikacin for at least 14 days. Exclusion criteria included acute illness (enrolment could be deferred), neurologic disability which may have prohibited reporting of pain, or a hemoglobin < 8 g/dL. Consecutively eligible children were recruited from the Brooklyn Chest Hospital, a provincial TB hospital which provides long-term care of children with drug-resistant and other complicated forms of TB in Cape Town, South Africa. A sample size of 12 participants was primarily based on pragmatic considerations of the expected number of eligible children. The treatment of MDR-TB was consistent with local and international guidance, and generally included 6–7 antituberculosis medications given for 12–18 months duration. Amikacin, a second-line injectable antituberculosis medication, was included in the regimen of most children with MDR-TB, and was given as an intramuscular injection 6 days each week for 2–6 months. Amikacin is recommended for MDR-TB treatment in adults and children, but is used off-label for this purpose.

Interventions

Each participant received two treatments, each on a single occasion. In treatment A, amikacin was administered without lidocaine; in treatment B, amikacin was administered with lidocaine. Participants were assigned 1:1 to receive treatment A or treatment B first (sequence 1 or sequence 2, respectively). Amikacin was available in 2 mL vials as a 500 mg/2 mL solution for injection (Fresenius, Midrand, South Africa), and was administered as an exact 15 mg/kg dose on the day of sampling. A pre-specified weight-banded dose of lidocaine (2% lidocaine solution for injection [20 mg/mL], Fresenius, Midrand, South Africa), within the range of 0.2–0.4 mg/kg/dose was drawn up into a syringe along with the amikacin, to be co-administered (see Table 1); this is well below the maximum safe dose of lidocaine for anesthesia of 3–4 mg/kg. Intramuscular injections were administered with a 21 gauge 1.5 inch needle in the dorsogluteal area on the opposite side as the previous day's injection, according to standard local practice.

Randomization and blinding

The randomization was generated by the study statistician using a computer generated list of random numbers with a permuted fixed block randomization having a block size of 4 to assign the order of injections. Allocations were placed in consecutively numbered, sealed, opaque envelopes (17). Upon enrolment of a participant, two unblinded study team members reviewed the allocation, and on the days of pharmacokinetic sampling, they prepared the amikacin injections with or without lidocaine according to the allocation.

Only these two study team members responsible for preparing the injections and the study statistician were unblinded. None of these unblinded team members participated in administration of the injections or in pain assessments. After preparation of the injections, opaque tape was placed around the syringe to ensure that small differences in volume of the injection would not be visible, to further ensure integrity of the blinding. The study participant and caregivers, and the remainder of the study team were blinded to the allocation.

Pharmacokinetic sampling

Pharmacokinetic sampling was completed from 2–16 weeks after starting treatment. On the day of sampling the amikacin dose was administered by the study team together with all the other oral TB medications in the child's MDR-TB regimen. One hour after TB medication was dosed HIV-infected children were given their antiretroviral drugs. Blood samples were collected pre-dose and then at 1, 2, 4, 6, and 8 hours after amikacin dosing into an EDTA-containing tube and placed on ice. Blood samples were centrifuged and plasma separated and frozen at –80 degrees Celsius within 30 minutes.

Amikacin plasma concentrations were measured using a commercial Particle Enhanced Turbidimetric-Inhibition Immunoassay (PETINIA) (Architect ci4100, Abbott Laboratories, Diagnostics Division, Abbott Park, IL.). The assay was valid over the range 2.0 – 50 µg/ml and quality controls were run daily to monitor the assay performance.

Data collection

Pain was assessed using the Wong-Baker FACES pain scale, a 5 point hedonic scale which has been extensively validated for assessing pain in children older than 7 years of age (18, 19). The pain scale was translated into Afrikaans and Xhosa, the most frequently used local languages. Using this scale, the children were asked by a study team member to rate the pain in the dorsogluteal area on the side of the day's IM injection. This was done before the injection, to account for pre-existing pain from previous injections, immediately after the injection, and then at 30 and 60 minutes post-injection. In order to account for pre-existing pain from previous daily injections, adjusted pain scores were calculated by subtracting the pain score taken just prior to the injection, from the pain score immediately after injection, and from the scores at 30 and 60 minutes after the injection. HIV status was determined by HIV ELISA testing in children >18 months of age, and HIV DNA PCR in those <18 months. Weight-for-age z-scores were calculated using the 1990 British growth curves (20). The study team monitored for adverse events related to the injections during the 60 minutes

post-injection. Adverse events were graded according to standard grading criteria (21) and attribution assessed by the study investigator.

Statistical methods

Demographic and clinical characteristics were summarized using descriptive statistics. Pharmacokinetic measures were estimated using non-compartmental analysis (NCA). Observed maximum plasma concentration ($C_{\max}$) and time to $C_{\max}$ ($T_{\max}$) were recorded directly from the concentration-time data. The area under the concentration time curve from 0–8 hours (AUC_{0-8}) was calculated using the linear trapezoidal rule. The $AUC_{(0-\infty)}$ was calculated using an exponential extension to the $AUC_{(0-8)}$. Half-life ($t_{1/2}$) was denoted as $\ln(2)/k_{el}$, where k_{el} (elimination rate constant) was the negative slope of the log-linear regression of the three final data points of the concentration-time curve. Pre-dose drug concentrations below the lower limit of quantification (BLQ) (2.0 µg/mL) were set to zero in the analysis. For post-dose concentrations that were BLQ, the first was set to ½ of the lower limit of quantification (LLOQ), and any subsequent were set to zero.

The primary outcome was adjusted pain scores post-injection. Secondary outcomes were $C_{\max}$, $AUC_{(0-8)}$, $AUC_{(0-\infty)}$ and the number of adverse events at least possibly related to the injection. The median and interquartile range (IQR) for adjusted pain scores immediately, 30 and 60 minutes after injection and pharmacokinetic parameters ($C_{\max}$, $AUC_{(0-8)}$, $AUC_{(0-\infty)}$, $T_{\max}$, and $t_{1/2}$) were reported by whether lidocaine was given. Comparisons for each variable (adjusted pain scores and pharmacokinetic measures) by lidocaine status were made using the Wilcoxon matched-pairs signed-ranks test. Geometric means, the exponentiated arithmetic means of log-transformed values, are often better estimators for comparing pharmacokinetic parameters, which are frequently positively skewed and log-normally distributed. Geometric mean ratios (GMR) were reported with 90% confidence intervals and p-values to determine if treatment status was associated with $C_{\max}$, $AUC_{(0-8)}$, $AUC_{(0-\infty)}$ or $T_{\max}$. A test drug is considered to be bioequivalent to a reference drug if the 90% confidence interval of the GMR of the AUC and $C_{\max}$ between the test and reference fall within 80%–125%. Carryover effects for pain and pharmacokinetic measures were assessed statistically using accepted methods, by comparing the mean and median values for the pharmacokinetic parameters and the adjusted pain score outcomes between the two sequences (AB vs BA) using t-tests and Wilcoxon rank sum tests, respectively (22). Pharmacokinetic parameters and other data analysis were performed using Stata 14.1 (StataCorp, 2015. *Stata Statistical Software Release 14*. College Station, TX: StataCorp LP.)

This study was approved by the Health Research Ethics Committee of Stellenbosch University (M12/08/043) and the University of Cape Town. Informed consent was provided by the parent or legal guardian and informed assent by the participant. The trial was registered with the Pan-African Clinical Trials registry, registration number PACTR201401000670381.

RESULTS

Between July 2013 and August 2015, 18 participants were screened, with 12 enrolled and randomized (see Figure, Supplemental Digital Content 1). Overall, the median age was 11.5

years (IQR: 9.9 – 13.4); other baseline characteristics are shown by sequence in Table 2. All randomized participants successfully completed the trial.

Adjusted pain scores are shown in Table 3. The median adjusted pain score immediately after the injection was lower when administered with lidocaine added: 1.0 (IQR 0.5–2.0) with lidocaine vs. 2.5 (1.0–4.0) without lidocaine ($p=0.004$); no significant carryover effects were detected. The median adjusted pain scores 30 and 60 minutes after the injection with lidocaine added were zero, however this was not statistically different compared with injections without lidocaine.

Summary pharmacokinetic measures are shown in Table 4 and Figure 1. All 24 pre-dose concentrations were BLQ, and sixteen 8-hour concentrations were BLQ. One participant had both 6-hour and 8-hour concentrations that were BLQ. There were no statistical differences in AUC_{0-8} , $AUC_{0-\infty}$ or C_{max} when administered with or without lidocaine (Table 3); no significant carryover effects were detected. GMRs for pharmacokinetic measures of interest are shown in Table 5. The 90% confidence intervals (CIs) for the GMRs are outside of what would be considered bioequivalence (0.80–1.25). Two participants had amikacin exposures that were statistical outliers (one for C_{max} , one for AUC_{0-8}); there was no clinical or laboratory explanation for these extreme values. No adverse events during the two pharmacokinetic sampling days were reported.

DISCUSSION

In this trial we have shown that the addition of lidocaine to amikacin injections in children and adolescents reduced immediate injection pain, was safe, and did not have substantial effects on amikacin pharmacokinetics.

Given previous research with lidocaine co-administered with ceftriaxone and penicillin, it is not surprising that pain was reduced with the addition of lidocaine. In those previous studies, however, lidocaine was used as a diluent to powder for injection, so the final volume for injection was not altered. The amikacin formulation routinely available in our study setting comes as a prepared solution for injection, so the volume for injection was larger when lidocaine was added. Although these additional volumes were relatively small, this may have reduced the anesthetic effect, as larger volumes would be expected to be associated with increased pain. When lidocaine is used as a diluent instead, it may be that the pain would be reduced even further. Some of the reported pain is likely related to the needle penetrating the skin. In this study we did not use a topical anesthetic agent, however it is possible that this would further reduce pain and would be an additional measure to improve the tolerability of these intramuscular injections. Although we did not include children aged <8 years in this study, there is no specific reason to believe that the addition of lidocaine to amikacin injections would not also reduce pain in younger children.

Pain at 30 and 60 minutes post-injection was not statistically different with lidocaine. It may be the study was under-powered to detect a difference. However, it is notable that the median adjusted pain score at these time points was zero on the occasion when administered with lidocaine, meaning that pain was no different than prior to the injection, and that in a

proportion of the patients the adjusted pain score was less than zero, meaning that after the injection pain was lower than before. It may be that the local anesthetic reduced the pre-existing pain related to past injections.

There were no significant differences between either the C_{max} or AUC with or without lidocaine. Establishing amikacin bioequivalence between the two treatments was not a pre-specified aim and the study was not powered to formally assess this. The 90% CIs for the GMRs did not fall between the targets for bioequivalence, which may be due to the disproportionate effect of a few outlier concentrations. Substantial between occasion variability of the rate and extent of absorption of injectable medications has been described (23, 24), and may explain some of the differences we observed between the two treatments in our small sample. Additional work, powered to demonstrate bioequivalence, would confirm more definitively that the addition of lidocaine does not significantly affect amikacin pharmacokinetics. However it is reassuring that there was not a statistical difference in key pharmacokinetic measures in our study.

Carryover effects were expected to be minimal both for pharmacokinetics, as amikacin is rapidly absorbed and eliminated, and for pain, as injections were always given on the alternate side as the previous day's injection and lidocaine has only an intermediate duration of action (hours). There were no adverse effects noted on the two study days related to the injections. As severe systemic adverse effects are associated with intravascular injection, careful adherence to IM injection administration practices is important. This includes choosing an appropriate injection site and ensuring that the needle is not in a vascular structure after penetration of the needle through the skin and prior to injection. The study was not designed to evaluate the safety of long-term daily intramuscular lidocaine administration. However to our knowledge there is no reason to suspect such adverse effects.

Based on these results, we would argue that the co-administration of lidocaine should become routine practice with intramuscular injections of the second-line antituberculosis drugs in both children and adults with MDR-TB. Lidocaine should be widely available, as it is used routinely for local anesthesia and is included in the WHO Model List of Essential Medicines. This is likely to be a minimal additional expense for TB programs, particularly given the potential of the intervention to reduce patients' pain and improve the tolerability of this treatment. Although elimination of the need for injectable treatment remains a longer-term priority, this is a safe, feasible and clinically impactful intervention that could immediately be implemented, which substantially reduces the pain associated with these very large number of injections, and could potentially improve the tolerability of MDR-TB treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Concentration-time profiles of intramuscular amikacin with and without lignocaine among children (n=12) treated for multidrug-resistant tuberculosis

Table 1

Weight-banded doses and volumes of lidocaine co-administered with amikacin intramuscular injections in children with multidrug-resistant tuberculosis

Body weight	2% lidocaine volume (mg) added	Lidocaine mg/kg dose, range	Amikacin (15 mg/kg) volume, range	Volume of combined injection, range
10 – <20kg	0.2 mL (4 mg)	0.2 – 0.4 mg/kg	0.6 – 1.2 mL	0.8 – 1.4 mL
20 – <30kg	0.3 mL (6 mg)	0.2 – 0.3 mg/kg	1.2 – 1.8 mL	1.5 – 2.1 mL
30 – < 40kg	0.4 mL (8 mg)	0.2 – 0.27 mg/kg	1.8 – 2.4 mL	2.2 – 2.8 mL
40 – <50kg	0.5 mL (10 mg)	0.2 – 0.25 mg/kg	2.4 – 3 mL	2.9 – 3.5 mL
50kg	0.5 mL (10 mg)	<0.2 mg/kg	3 mL	3.5 mL

Table 2

Baseline characteristics by sequence for children routinely treated with amikacin for multidrug-resistant (MDR) tuberculosis (TB)

	Sequence 1 (Without lidocaine then with lidocaine) (n=6)	Sequence 2 (With lidocaine then without lidocaine) (n=6)
Median age at enrolment (IQR)	10.3 (9.8–11.4)	13.4 (11.7–14.5)
Male gender (%)	6 (100)	2 (33)
HIV-infected (%)	3 (50)	0 (0)
WAZ < -2 (%)	3 (50)	1 (17)
Median weeks on MDR-TB treatment (IQR)	6.4 (3.0–15.9)	9.5 (5.9–11.7)

IQR=interquartile range, WAZ=weight-for-age z-score

Table 3

Adjusted pain scores among children with multidrug-resistant tuberculosis (n=12) receiving amikacin injections with and without added lidocaine

	Treatment A (without added lidocaine)	Treatment B (with added lidocaine)	p-value *
Median adjusted pain score, immediately after injection (IQR)	2.5 (1 to 4)	1 (0.5 to 2)	0.004
Median adjusted pain score, 30 minutes post-injections (IQR)	1 (0 to 1.5)	0 (−0.5 to 0.5)	0.107
Median adjusted pain score, 60 minutes post injections (IQR)	1 (0 to 1)	0 (−1 to 0.5)	0.075

IQR = interquartile range

* Wilcoxon matched-pairs signed-ranks test

Table 4

Summary statistics for amikacin (15 mg/kg) pharmacokinetic parameters with and without lidocaine among children with multidrug-resistant tuberculosis (n=12)

Pharmacokinetic parameter	Treatment A	Treatment B	p-values [*]
	Without lidocaine, median (IQR)	With lidocaine, median (IQR)	
AUC ₀₋₈ (µg* h/mL)	103.3 (81.7–135.0)	109.0 (84.7–121.3)	0.814
AUC _{0-∞} (µg* h/mL)	107.5 (83.8–136.8)	111.3 (86.8–126.4)	0.754
C _{max} (µg* h/mL)	34.1 (25.6–46.4)	36.7 (34.1–40.5)	0.638
t _{1/2} (h)	1.28 (1.14–1.49)	1.50 (1.27–1.62)	0.182
T _{max} (h)	1 (1.0–1.0)	1 (1.0–1.0)	0.157

^{*} Wilcoxon matched-pairs signed-ranks test

AUC=area under the concentration time curve, C_{max}=maximum plasma concentration, t_{1/2}=half-life, T_{max}=time to C_{max}

Table 5

Geometric means with and without lidocaine, geometric mean ratio and 90% confidence interval for amikacin (15 mg/kg) pharmacokinetic parameters (n=12)

Pharmacokinetic parameter	Geometric mean (GM)		GM Ratio (90% CI)*
	Treatment A Without lidocaine	Treatment B With lidocaine	
AUC ₀₋₈	93.8	110.6	1.18 (0.89–1.56)
AUC _{0-∞}	96.2	114.3	1.19 (0.90–1.57)
C _{max}	31.8	37.6	1.18 (0.92–1.52)

* Treatment B/Treatment A

AUC=area under the concentration time curve; C_{max}=maximum plasma concentration; CI=confidence interval