**Seizures and Quinolone Antibiotics in Children: A Systematic Review of Adverse Events**

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# **ABSTRACT**

**Objective**

Quinolone antibiotics have a broad spectrum of activity including against Gram negative organisms (especially Pseudomonas) but their use has been associated with the development of seizures. Our objective was to evaluate the association between the administration of quinolones and seizures for three groups of children; those with epilepsy; those with other central nervous system (CNS) disorders; and those without any CNS disorder.

**Design**

We conducted a systematic review of the MEDLINE, EMBASE and CENTRAL databases. Any studies reporting the administration of quinolones to children and including a methodology for identifying or reporting adverse events (AEs) were identified by two authors who worked independently. Data relating to study characteristics (including population, intervention, comparison and outcome data) and study quality (including the quality of adverse event reporting) were extracted.

**Results**

We identified 146 studies involving 21,884 children. No studies reported involving children with epilepsy and 21 studies reported the involvement of 317 children with CNS disorders. 2/317 (0.63%) children with CNS disorders developed seizures and at least 5/21,567 (0.023%) children without CNS pathology were reported to have developed seizures. The quality of adverse event reporting in included studies was low. Only 8/140 (5.71%) included studies provided details of a methodology for actively identifying adverse neurological events.

**Conclusions**

Even for children with CNS disorders the risk of developing seizures in association with the use of quinolones seems to be low. Further evaluations of quinolone use in children should include methodologies for actively identifying and reporting adverse neurological events.

**NON-TECHNICAL SUMMARY**

A class of antibiotics called the quinolones contain structures which may cause seizures (fits) in susceptible individuals. These can be very useful antibiotics so weighing up the risks and benefits in children who may be prone to seizures can be challenging. Our review of 140 studies shows that these risks may be very small, however these results should be interpreted with caution, as the studies we identified were generally not well designed for detecting whether or not quinolones do cause seizures.

**INTRODUCTION**

Quinolone and fluoroquinolone antibiotics are bacteriocidal agents that target bacterial DNA replication. They have a broad spectrum of activity against both Gram-negative and Gram-positive organisms, high bioavailability from oral preparations, and are the only oral anti-pseudomonal agent. Children with neurological disorders are recognized to be at higher risk of developing infections that would often be susceptible to treatment with quinolone antibiotics [1, 2]. However, there are concerns that quinolones may lower the seizure threshold and, in the US and UK, quinolones (such as ciprofloxacin) are only licensed for use in children in certain circumstances. Examples include the treatment of complicated urinary tract infections and pseudomonal infections in cystic fibrosis [3] [4].

Concerns that quinolones may lower the threshold for seizures have been linked to their chemical structure. Norfloxacin and ciprofloxacin contain Gamma-Aminobutyric Acid (GABA)-like structures in substituents at their 7 positions. These structures may act as antagonists of GABA receptors, thereby increasing the likelihood of seizures, as demonstrated using mouse models [5-7]. However these findings have not been reproduced in studies investigating the administration of quinolones to adults [8, 9]. In children, data from the UK Medicines and Healthcare products Regulatory Agency (MHRA) adverse events “yellow card” reporting service also provided limited evidence associating quinolone use with seizures in children. A review of MHRA drug analysis profiles identified 13 submissions reporting non-fatal seizures in children associated with the use of quinolones since 1987 (identified using a search of MHRA drug analysis profiles[10]).

The aim of this study was to review the association between the use of quinolones and the development of seizures in children, in order to help clinicians assess the risks and benefits of their use. These risks were evaluated using a systematic review of published literature designed to identify any reports of seizures associated with the use of quinolones in three groups of children:

1. Those known to have epilepsy
2. Those at higher risk of developing seizures due to associated CNS disorders of any aetiology (including infectious, congenital, developmental, traumatic or neoplastic disorders).
3. Those without a history of epilepsy or other CNS disorders.

# **METHODS**

The Medline, Embase, Pubmed and Cochrane Central Register of Controlled trials (CENTRAL) databases were searched (from inception until November 2017) to identify studies reporting the administration of quinolones to children (17 years or younger), where the authors also reported an assessment of safety through the active or passive identification of adverse events (see online supplementary file for full search strategy). Two authors independently screened the titles and abstracts to identify full texts for consideration for inclusion in the review. We included any studies meeting the inclusion criteria including randomised-controlled trials, observational studies and case reports.

We excluded studies where quinolones were not administered either orally or intravenously and due to time and resource constraints we excluded non-English language studies.

Bibliographies of systematic reviews, meta-analyses and review papers identified from the initial strategy were subsequently hand searched to identify additional studies that met the inclusion criteria.

The protocol for this investigation was based on accepted methodology for identifying and reporting adverse events using systematic review and was agreed a priori [11, 12]. Following the initial searches and further discussion amongst the group we agreed to exclude studies from the final analysis if

* They included children but it was not possible to separate data relating to children and adults from the published results.
* Studies described a methodology that would preclude investigators from identifying seizures as an associated adverse event; for example, using follow up X-rays to identify joint pathology or searching registries for episodes of joint pathology following quinolone administration

In keeping with a recognised framework for using systematic review methodology to report adverse events (AEs) (where AEs are often identified and reported using heterogeneous methods)[11] we included any descriptions of seizures associated with the use of quinolones as the primary outcome of interest. A secondary evaluation, that included the assessment of factors such as the likelihood that reported seizures were related to the administration of quinolones, was completed as part of the quality assessment and is described below.

## **Data Extraction**

Included papers were interrogated to identify study characteristics, population, intervention, comparison and outcome (PICO) data (including details of individuals known to have epilepsy or other CNS disorders) and study methodology. Randomised controlled trials were assessed for bias based on evidence of the quality of randomisation, allocation concealment and blinding. The quality of AE reporting was assessed for all studies based on the rigour with which investigators described methodologies for actively identifying and reporting AEs. We also noted whether investigators had reported a methodology for identifying neurological AEs. When seizures were reported we assessed whether the investigators had used a recognised methodology for determining the likelihood that they were causally related to the use of quinolones.

## **Data Analysis**

Given the likely heterogeneity of studies eligible for inclusion in the review we planned to report our findings using a narrative synthesis.

# **RESULTS**

The search strategy identified 140 studies for inclusion in the review (see Figure 1. PRISMA flow chart for full details of excluded studies; see online supplementary file for a list of included and excluded studies (studies excluded following a review of the full text)).

Thirty-two studies were randomised-controlled trials (RCTs), 75 were observational studies, and 33 were case reports or case series. The included studies reported data relating to 33,718 participants, 21,884 of whom were children who had been administered quinolones in 22,714 treatment episodes. Included studies involved children of all ages, ranging from preterm infants with a post-mestrual age of 24/40 weeks up to 17 year olds (see Study Characteristics table in online supplementary file for summarised PICO data).

## **Types of Quinolones Administered to the Study Population**

Ciprofloxacin was the most widely used quinolone (n = 16,633), followed by levofloxacin (n = 2,739) and gatifloxacin (n = 1,157) (see table 1 for full list of administered antibiotics and dosing ranges prescribed).

| **Quinolone** | **Number of children who received quinolone** | **Dosing and administration information** |
| --- | --- | --- |
| Ciprofloxacin | 16,633 | IV - dosing range 8-30mg/Kg/Day up to 500mg/Day  PO - 10-40 mg/Kg/Day or up to 1·5g/Day |
| Levofloxacin | 2,793 | IV - dosing range 7-25 mg/Kg/Day up to 500mg/Day  PO - 10-40 mg/Kg/Day |
| Gatifloxacin | 1,157 | PO - 10-15 mg/Kg/Day |
| Ofloxacin | 790 | PO - 10-40 mg/Kg/Day up to 400mg/Day |
| Trovofloxacin | 162 | IV - 5mg/Kg/Day |
| Moxifloxacin | 32 | PO - 10mg/Kg/Day up to 400mg/Day |
| Nalidixic Acid | 30 | PO - 50-220 mg/Day |
| Norfloxacin | 24 | PO - 20-30 mg/Day |
| Pefloxacin | 12 | IV - 12 mg/Day  PO – 12.5mg/Kg/Day |

**Table 1. Dosing ranges and administration routes for included quinolones** (IV = Intravenous administration, PO = oral administration)

## **Overall Result**

The administration of oral or intravenous quinolones was only rarely associated with the development of seizures (overall incidence of confirmed, reported seizures 6/21,884 participants (0.03% of children)).

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## **Studies involving children with epilepsy**

No studies reported the involvement of children known to have epilepsy.

## **Studies involving children with CNS disorders**

21 studies reported the inclusion of 317 children with CNS disorders (see Table 3. Summary of indications and underlying conditions described in included studies). Bacterial meningitis was the most frequently reported CNS disorder (n = 237), followed by CNS malignancies (n = 29), and infants with grade III or IV Intraventricular Haemorrhage (IVH) (n = 19).  In one study, 22 children with neurologic disorders not otherwise specified were reported to have received quinolones, but no further details on their CNS disorder were provided.

Seizures occurred in 2/317 children who were reported to have an associated CNS disorder. One child had confirmed *H. influenzae* meningitis, and authors of the case report commented that the prior administration of trovofloxacin was unlikely to have been the cause of the child’s seizure. This occurred 11 days after trovofloxacin had been discontinued. One child had leukaemia and Cryptococcal meningitis, but authors did not comment on an association between gatifloxacin and the seizure. Neither case report indicated a standardized methodology for grading the likelihood that seizures were related to the administration of quinolones.

## **Studies Involving Children Without CNS Pathology**

119 studies reported the inclusion of 21,567 children without reported CNS disorders (see table 3 for a summary of the indications for the use of quinolones). At least 4/21,567 (0.023%) children developed seizures in association with the administration of quinolones; their clinical features are summarised in table 2. In one study reported as a conference abstract, involving 165 neonates treated with quinolones, the authors reported that some infants developed seizures however specific details regarding the numbers of affected infants were not provided [13].

| **Children with CNS Disorders Who Developed Seizures** | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age** | **M/F** | **Medical History** | **Reason for quinolone use** | **Quinolone** | **Dosing and administration** | **Association with quinolone use** | **Quinolone discontinued** | **Outcome** |
| 8m | M | Pneumonia, herpes stomatitis, hepatitis, diseminated intravascular co-agulation. | *Haemophilus* meninigitis | Trovofloxacin | 5mg/Kg loading dose, then 2.5mg/Kg 12 hourly IV | Unlikely - seizure developed 11 days after stopping trovafloxacin | N | No long term morbidity |
| N/A | N/A | Leukaemia and *Cryptococcus neoformans* meningitis | Febrile neutropaenia | Gatifloxacin | 15mg/Kg 24 hourly PO | N/A | N/A | N/A |
| **Children Without CNS Disorders Who Developed Seizures** | | | | | | | | |
| 1·25 years | M | Pneumonia | Pneumonia | Ciprofloxacin | 10mg/Kg 12 hourly IV | Possible | N/A | No long term morbidity |
| 3m 24d | F | Bronchiolitis | Pneumonia | Ciprofloxacin | 10mg/Kg 12 hourly IV | Unlikely | Y | No long term morbidity |
| N/A | N/A | N/A | Pneumonia | Levofloxacin | 10mg/Kg 12 hourly - administration details not provided | Possible - described as a “febrile convulsion” | N/A | N/A |
| 2·5 years | N/A | N/A | *S. flexneri* enteritis | Ciprofloxacin | 10mg/Kg 12 hourly PO | N/A | N/A | N/A |

**Table 2. Characteristics of children who presented with seizures in association with the use of quinolones (N/A = data not available)**

In two of the reported cases of seizures the reporting clinicians felt that the seizure was possibly related to the use of quinolones, in one case this was felt to be unlikely (one child had presented with seizures prior to initiation of ciprofloxacin) and in one case no comment was made with regards to the possibility of a causal relationship. In one case the prescribed quinolone was withheld following the seizure episode and in four cases it was not clear whether the quinolone therapy was discontinued by the investigators. None of the authors reported the use of a standardised system for grading the likelihood that the described AEs were related to the use of quinolones.

| **Type of infection** | **Number of children** | **Underlying Condition** | **Number of Children** |
| --- | --- | --- | --- |
| Gastro-intestinal infection including enteric fever | 6043 | Cystic fibrosis - most cases with associated pulmonary exacerbation | 995 |
| Otitis Media | 2706 | Paediatric cancers | 1019 |
| Community Acquired Pneumonia | 1935 | Post haematopoetic stem cell transplantation | 265 |
| Prophylaxis | 979 | Chronic renal disease | 20 |
| Febrile neutropenia | 593 | Neurologic disorders | 22 |
| Neonatal sepsis | 591 | Intra-ventricular Haemorrhage (Gr III-IV) | 19 |
| Central nervous system | 245 | CNS malignancy | 29 |
| Cellulitis | 227 | Congenital cyanotic heart disease | 2 |
| Tuberculosis | 67 | Head Injury | 2 |
| Bacteraemia | 100 | Leukaemia and *Cryptococcus neoformans* meningitis | 1 |
| BK Viraemia | 19 | Myelitis | 1 |
| Bone or Joint | 23 | Bare lymphocyte Syndrome | 1 |
| Cholangitis | 13 | Inflammatory bowel disease | 1 |
| Tularaemia | 12 | Major Histocompatibility Complex class II deficiency | 1 |
| Infection of prosthetic cardiac device | 2 | Sacral agenesis | 1 |
| Rhinoscleroma | 1 |  |  |
| Other/indications not described in detail | 7343 |  |  |

**Table 3. Summary of indications and underlying conditions described in included studies**

## **Other Adverse Events**

The most frequently reported adverse events described in association with the use of quinolones included nausea and vomiting (n = 916, 4.60% of participants), diarrhoea (n = 661, 3.34% of participants) and rash (n = 606, 3.03% of participants) (see table 3 for a summary of the most frequently reported adverse events). Joint symptoms were identified in 482 children (2.41% of participants). We note that seizures were reported less frequently than other adverse events including episodes of acute kidney injury (n = 48 (0.22% children administered quinolones (A summary of reported adverse events is presented in Table 4).

| **Symptom** | **Number of children Affected (%)** |
| --- | --- |
| Nausea and Vomiting | 916 (4.6%) |
| Diarrhoea | 661 (3.3%) |
| Rash | 606 (3.0%) |
| Joint Pain | 482 (2.4%) |
| Elevated Hepatic Enzymes | 228 (1.1%) |
| Abdominal Pain | 200 (1.0%) |
| Acute Kidney Injury | 48 (0.2%) |

**Table 4. Most frequently reported adverse events**

## **Quality of Adverse Event Reporting**

All of the studies included in the analysis involved either active or passive monitoring for adverse events, or alternatively the authors reported the presence or absence of AEs in the results or discussion sections of the paper. The authors of 92/140 (65.7%) included studies reported that AEs were actively sought during their investigation of the use of quinolones. The authors of 61/140 (43.6%) studies provided some methodological detail relating to the active identification of AEs. However only 8/140 (5.71%) included studies provided details of a methodology describing the active identification of neurological adverse events including seizures. 34/140 (24.3%) of studies described methodologies for the active identification of AEs relating to joint pathology or abnormal growth.

# **DISCUSSION**

To our knowledge this is the first systematic review designed to investigate the potential association between the use of quinolones and seizures in children. Evaluating the risks and benefits of using quinolones for children with CNS disorders may be particularly important because this group are likely to be at higher risk of developing resistant, Gram negative or hospital acquired infections [1, 2]. In these cases, the benefits of using highly bio-available, broad spectrum quinolone antibiotics need to be balanced with a consideration of their risks.

A comparison of the incidence of seizures in children who were administered quinolones and reported to have associated CNS disorders (2/317 (0.63%)), with the reported incidence of seizures in children who did not have associated CNS disorders (4/21,567 (0.02%)), suggests that the risk of developing seizures seems to be small for both groups. However, this review has a number of limitations.

One limitation is that the majority of eligible studies were not designed with robust methods for identifying adverse neurological events such as seizures. Only 8/140 (5.71%) studies provided detail of a specific methodology for prospectively identifying these types of AEs. Another limitation is that none of the identified investigations reported the inclusion of children with epilepsy. Furthermore, only a minority of studies included participants who may have been predisposed to developing seizures due to central nervous system (CNS) disorders including CNS infections, neuro-disability or brain injuries.

In addition to limitations relating to the active identification of adverse events in the included studies, we also identified limitations relating to the selective reporting of outcomes, or incomplete reporting of AE data in certain studies (this occurred despite the requirement for all included studies to report the results of an adverse events analysis, see Study Quality Summary Table for further details).The study that included the largest number of participants with associated CNS disorders was a randomised trial comparing trovofloxacin (now withdrawn from use) with ceftriaxone, with or without vancomycin, for the treatment of meningitis [14]. The study included 311 children, 162 of whom were administered trovofloxacin. Although the authors reported a methodology for actively identifying seizures in participants there was incomplete reporting of AEs (the authors reported a total of 437 AEs in the trovofloxacin group but only provided detail regarding 99 of these in the published report). In another study, reported as a conference abstract, seizures were identified in an unspecified number of infants but the authors provided no details regarding the total numbers affected, or whether the seizures were felt to be related to the administration of quinolones [13](attempts to contact the study authors to obtain more detailed data regarding the outcomes of their investigation were made during the completion of this review).

**CONCLUSION**

The risk of developing seizures in association with the use of quinolones seems to be small. Future studies involving the use of quinolones in children would benefit from robust methodologies for actively identifying and reporting adverse neurological events. This would help to further quantify the risks associated with the use of quinolone therapy for children who may otherwise benefit from their use.

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**Competing Interests**

None Declared.

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