BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2009.03580.x

Superior palatability of crushed lercanidipine compared with amlodipine among children

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Keywords
amlodipine, child, hypertension, lercanidipine, palatability

Received
28 July 2009

Accepted
28 September 2009

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Among children, medication palatability is crucial for adherence to therapeutic regimen.
- Since there is a lack of appropriate formulations for children prescribed drugs originally designed for adults, parents crush available tablets and administer the medication mixed with solid food or a palatable drink.
- Crushed amlodipine, a very popular calcium channel blocker, is bitter and unpalatable.

WHAT THIS STUDY ADDS

- From the perspective of the child with arterial hypertension, the taste of pulverized lercanidipine is superior to that of pulverized amlodipine.

AIMS

To compare the taste of equivalent doses of pulverized amlodipine and lercanidipine, two calcium channel blockers, among children with kidney disease.

METHODS

Each child received a test dose of 1 mg of amlodipine besylate and 2 mg of lercanidipine in a single-blinded fashion. Children indicated their preference by pointing to the appropriate face on a visual analogue scale (VAS) that depicts five degrees of pleasure.

RESULTS

The VAS palatability score assigned to lercanidipine was higher than that assigned to amlodipine both in nine children 4–7 years of age ($P < 0.005$) and in 10 children 8–11 years of age ($P < 0.005$). The preference for lercanidipine was statistically significant in both girls ($P < 0.02$) and boys ($P < 0.001$) and in both children initially presented amlodipine ($P < 0.005$) and children initially presented lercanidipine ($P < 0.005$).

CONCLUSIONS

There is a lack of appropriate formulations for children prescribed drugs originally designed for adults, such as calcium channel blockers. Parents therefore crush available tablets and administer the medication mixed with solid food or a palatable drink. From the perspective of the child, the taste of pulverized lercanidipine is superior to that of pulverized amlodipine.

Introduction

The dihydropyridine calcium channel blocker amlodipine is currently very popular for treatment of arterial hypertension in both adults [1] and children [2] because it provides adequate blood pressure reduction when dosed once daily. Studies in hypertensive adults indicate that the new dihydropyridine calcium channel blocker lercanidipine

dosed once daily is as effective as amlodipine but is less frequently associated with a tendency towards peripheral oedema [3, 4]. However, no information is available so far on the use of lercanidipine in childhood.

A problem that often affects drugs originally designed for use in adults, such as calcium channel blockers, is the lack of formulations appropriate for childhood. Parents therefore crush available tablets and administer the medication mixed with solid food or a palatable drink [5, 6]. Some time ago, we switched to lercanidipine a 5-year-old child with hypertension and peripheral oedema caused by amlodipine. Interestingly, the child indicated a clear preference for the neutral taste of crushed lercanidipine. The observation prompted us to compare the taste of equivalent doses of pulverized amlodipine and lercanidipine among children with kidney disease.

Subjects and methods

Eligible for the single-blind taste comparison, which had been approved by the local ethics committees, were 10 children 4–7 years of age and 10 children 8–11 years of age with acute or chronic kidney disease and systolic or diastolic blood pressure ≥95th percentile [7] if they were willing to comply with appropriate instructions necessary to complete the comparison, which was not commercially sponsored.

Each study consisted of one session lasting 15–20 min. After obtaining written informed consent, the investigator accompanied each child to a private test area and described procedures and rating scales. It was explained to the children that they would be asked 'how much did you like the taste of this medicine' and encouraged to indicate their preference by pointing to the appropriate face on a visual analogue scale (VAS) that depicts five degrees of pleasure [6]: 'really good' (=5), 'good' (=4), 'not sure' (=3), 'bad' (=2) and 'really bad' (=1). The explanation was repeated if the child did not understand. Each child received a test dose of 1 mg of amlodipine besylate (Norvasc®) and 2 mg of lercanidipine (Zanidip®) into the oral cavity from an opened capsule shell. A pharmacist had crushed and pulverized commercially available tablets of amlodipine and lercanidipine and prepared capsule shells containing 1 and 2 mg, respectively, of active substance. No attempt was made to disguise the colour of the two pulverized preparations (amlodipine besylate is white and lercanidipine yellow).

The two agents had been identified to each child by letter only. Between tastings of the two drugs, each child received a cracker to eat and rinsed the mouth to remove any residual taste from the previous drug. After each test dose, the children rated the taste by pointing to the appropriate face. Following completion of the tasting phase, each child remained at the study site for 1 h to monitor for any adverse events. A follow-up telephone call to the family was also made 1–3 days after the test to evaluate possible adverse events.

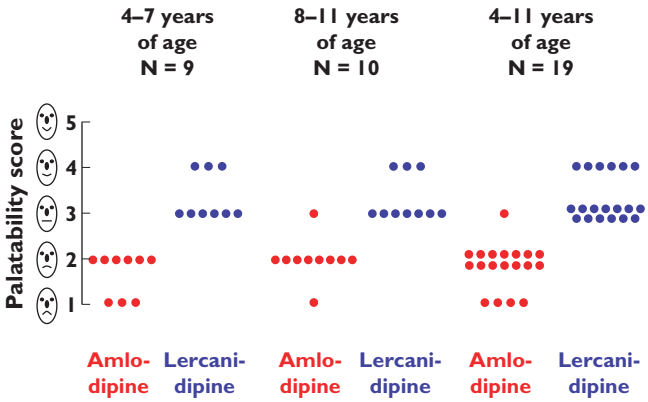

Figure 1

Visual analogue scale palatability score of pulverized amlodipine (1 mg) and pulverized lercanidipine (2 mg) in children with acute or chronic kidney disease. The palatability score assigned to lercanidipine was higher than that assigned to amlodipine in nine children 4–7 years old ($P < 0.005$), in 10 children 8–11 years old ($P < 0.005$) and in the cumulated group of 19 children 4–11 years old ($P < 0.001$)

Within both the group 4–7 years old and that 8–11 years old, patients were randomized by means of a computer-generated list to balance the order of presentation between the two test medications so that each medication was tasted first an equal number of times. The taste scores from the VAS were analysed using the nonparametric Wilcoxon matched paired signed rank test [6]. Significance was assumed when $P < 0.05$ (two-tailed).

Results

Between November 2008 and June 2009, 10 patients 4–7 years of age (three girls and seven boys) and 10 patients 8–11 years of age (four girls and six boys) with arterial hypertension were enrolled in the test. The underlying kidney disease was acute in five and chronic in 15 cases. Nine of the 15 patients with chronic kidney disease were on antihypertensive medication with a variety of drugs, including angiotensin II receptor blockers ($n = 4$), converting enzyme inhibitors ($n = 2$), diuretics ($n = 2$) and angiotensin II receptor blockers associated with a diuretic ($n = 1$).

A 4-year-old boy initially presented amlodipine was not able to express his taste preferences. The results of the taste testing in the remaining 19 children appear in Figure 1. Although none of the children graded the palatability score of either 1 mg of crushed amlodipine or 2 mg of crushed lercanidipine as really good, 18 of the 19 children assigned a better VAS palatability score to lercanidipine than to amlodipine ($P < 0.001$). The tendency was significant both in the group of nine children 4–7 years old

($P < 0.005$) and in that of 10 children 8–11 years old ($P < 0.005$). The preference for lercanidipine was statistically significant both in seven girls ($P < 0.02$) as well as in 12 boys ($P < 0.001$) and both in nine children initially presented amlodipine ($P < 0.005$) and in 10 children initially presented lercanidipine ($P < 0.005$). Finally, the preference for lercanidipine was statistically significant both in nine children on antihypertensive medication ($P < 0.005$) and in 10 without antihypertensive medication ($P < 0.005$).

No adverse effects were noted during, immediately after or 1–3 days after the taste tests.

Discussion

The undisputed importance of taste of paediatric oral formulations often presents relevant challenges to the pharmaceutical scientist. Unlike in adults, where solid forms are acceptable to the vast majority of patients, potential paediatric patients include newborns, infants, children and adolescents, who, as such, have widely varying needs. The development of multiple dosage forms for different ages is rarely commercially viable, and liquid formulations, which can be given to a broad age group, present particular pharmaceutical challenges. For example, taste masking a bitter-tasting drug is a major hurdle that is often costly and not totally achievable [5, 6]. The present single-blind comparison indicates that, from the point of view of children 4–7 and 8–11 years old affected by kidney disease, the taste of 2 mg of pulverized lercanidipine is superior to that of 1 mg of pulverized amlodipine besylate. The preference is probably related to the neutral taste of lercanidipine and to the bitter taste of amlodipine besylate. The preliminary investigation did not address the bioavailability of crushed lercanidipine considering that antihypertensive agents administered as crushed or conventional whole tablets are considered similarly effective in childhood [8].

We assessed the taste and smell acceptability of amlodipine and lercanidipine among children with kidney disease in a dose-equivalent way, considering that in adults amlodipine 5 mg once daily is approximately as effective as lercanidipine 10 mg, and amlodipine 10 mg as effective as lercanidipine 20 mg in reducing blood pressure [3, 4]. We did not compare pulverized lercanidipine, which has been approved for administration once a day, with agents like isradipine, which is administered three times a day [2], or with drugs like felodipine and nifedipine with sustained-release technologies that can reduce administration frequency to once a day [2], because manipulations such as cutting, crushing, or opening destroy their release characteristics.

A simple suspension of crushed tablets of amlodipine is used for patients who are unable to swallow tablets because its bioavailability is similar to that of tablets and likely to be stable for approximately 2 months when stored frozen in plastic prescription bottles [9, 10]. Unfortunately, this suspension is very unpalatable [10].

Considering that in the present paediatric experience lercanidipine was noted to have an agreeable palatability and that in adults this agent exhibits a superior side-effect profile relative to other dihydropyridine calcium channel blockers, paediatric clinical trials with lercanidipine are urgently needed.

Competing interests

None to declare.

Ma.R. is currently supported by a scholarship of the Ettore e Valeria Rossi Foundation.

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