Retrospective compilation of Olpadronate (OPD) adverse events:

Determination of dose of exposition (DOE) until the first adverse event occurrence

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ABSTRACT

Introduction

Bisphosphonates such as OPD are used in the treatment of skeletal disorders such as Paget´s bone disease and osteoporosis. But new indications are under development, therefore safe schedules are on demand. As intermittent schedules may be an option, we hereby report a compilation of OPD adverse effects aiming to estimate a specific exposition free of adverse events, by either I.V. or oral routes.

Methods

Adverse events were compiled retrospectively from a series of patients having Paget´s bone disease and treated with OPD at a university hospital in which the drug was authorized. Doses ranged from 4 - 8 mg/day I.V., and/or 100 - 200 mg/day orally. The OPD exposition until the first event (DOE) was calculated using the formula: ([daily dose multiplied by treatment duration until first adverse event reported] divided by body weight). The outcome was further divided by the bioavailability rate 0.035 when the administration had been orally . Student´s t test was used for the statistical analysis.

Results

One hundred patients, aged 60.8 ± 10.6 years (39 females) were included. More frequent adverse events were hypocalcemia (59% total sample), flu like (23%), leukopenia (16%), fever (15%), phlebitis (8%), headache (4%), somatic pain (7%), hypersensitivity (2%), and dizziness (2%). DOE after I.V. administration was significantly lower than after oral route for hypocalcemia (0.20 vs 0.33mg/Kg; $p<0.05$) and for flu like (0.09 vs. 0.17mg/Kg; $p<0.05$) and no significant differences in oral versus I.V. DOE (0.23 vs. 0.19mg/Kg) were observed for leukopenia ($p>0.05$).

Conclusion

The estimation of OPD DOE may help in the design of comfortable safe therapeutic schemes by providing intermittent oral and /or I.V. schedules best tolerated.

Introduction

- Bisphosphonates including olpadronate, are used in the treatment of skeletal disorders such as Paget bone disease.
- Olpadronate adverse events may show differences between dose exposition and the route of administration (1-4).
- The aim of this study was to determine the olpadronate tolerance profile. Specifically the dose of exposition in relation to the appearance of adverse events after oral and/or intravenous administrations.

Methods

- Patients with Paget bone disease (n=100), treated with olpadronate in doses from 4 to 8 mg/day IV (intravenous), and/or 100 to 200 mg/day orally were included. Time range of treatment duration was 5-13 days for IV administration, and 10 to 120 days for oral.
- Dose of exposition (DOE) was calculated for estimate the dose schedule of olpadronate free of adverse events, and was compared for IV and oral administration.
- The estimation of DOE was calculated using the formula: (daily dose divided by body weight) x treatment duration until the given adverse effect, and multiplied by the bioavailability (0.035 for oral administration only): [(D/b.w)x days till AE] X BA (5).
- Student t test was used for the statistical analysis.

Definitions

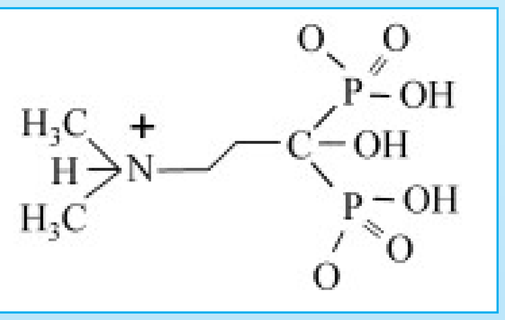
- Dose Exposition: Amount of drug accumulated in the body until the adverse event detection/perception.

Intravenous DOE = [(daily dose/ b.w.)x days till AE*]

Oral DOE = [(daily dose mg/kg)x treatment duration*]x 0.035

*Number of days between the first dose and the first day of a given adverse event occurrence

Olpadronate chemical structure: [3-(dimethylamino)-1-hydroxy propylidene] bisphosponate



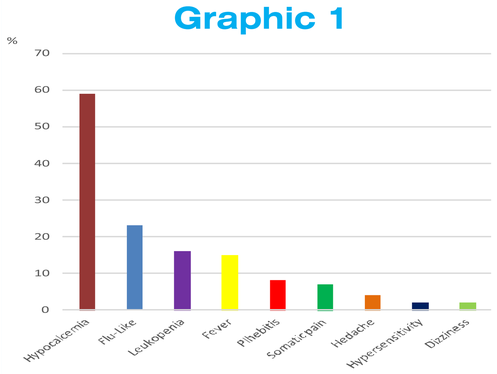
Results

Table 1

Variable	Mean ± SD
Age	60.81± 10.63 years
Body weight (kg)	79.37 ± 13.62 (Kg)
Bone Alkaline Phosphatase	299.83 ± 319,2 u/l
Plasma Alkaline Phosphatase	96.26 ± 27.5 u/l

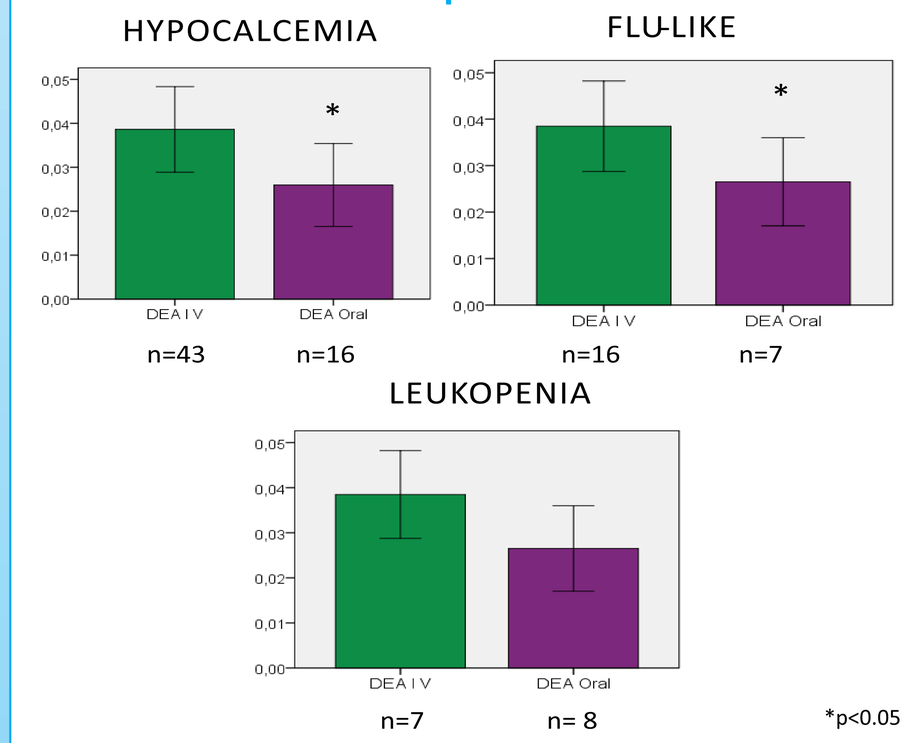
Clinical and demographic variables at basal in 100 patients with Paget bone disease

Graphic 1



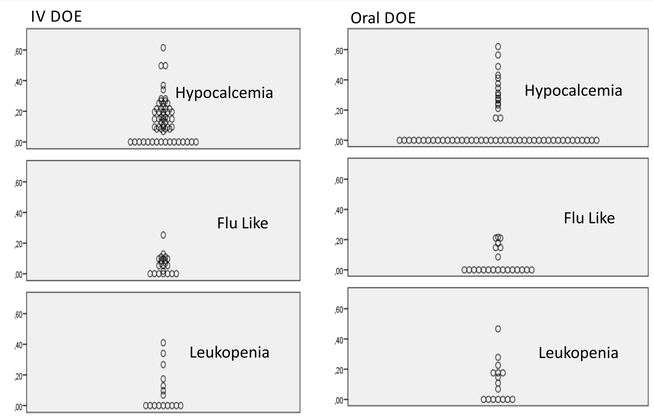
- One hundred patients, 39 females and 61 males, age 60.81 ± 10.63 years, were included.
- More frequent adverse events were hypocalcemia (59%), flu like (23%), leukopenia (16%), fever (15%), phlebitis (8%), somatic pain (7%), headache (4%), hypersensitivity (2%), and dizziness (2%)

Graphic 2



*p<0.05

Dose of Exposition (DOE) for oral versus IV (intravenous) olpadronate administration in subjects with Paget bone disease. DOE for IV administration was significantly lower than oral administration for hypocalcemia (0.20 vs 0.33 mg/kg) and flu like (0.09 vs. 0.17 mg/kg) ($p<0.05$) and no significant differences in oral versus IV DOE (0.23 vs. 0.19 mg/kg) were observed for leukopenia ($p>0.05$). Hypocalcemia is a consequence of the olpadronate anti-resorption activity.
Flu like constitutes an acute phase reaction syndrome and leukopenia is characterized by a quantitative non critical and reversible reduction of white blood count cells citotoxicity.



Graphic 3

Olpadronate more frequent adverse events distribution according IV DOE and oral DOE in 100 patients with Paget bone disease

Conclusions

The observation of a group of patients receiving continuous doses of olpadronate allows the detection of common adverse events. It also allows to estimate the exposition to the dose (DOE) free of such effects.

The estimation of DOE may help designing more safe therapeutic schemes for oral and intravenous intermittent administration of olpadronate.

References

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