Research paper

The use of bisphosphonates in women prior to or during pregnancy and lactation

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ABSTRACT

OBJECTIVE: The unique pharmacokinetics of bisphosphonates (BPs) in conjunction with their use by an increasing number of women at reproductive age has raised serious concerns about their safety during pregnancy and lactation. Bisphosphonates cross the placenta. Animal studies have shown adverse effects on both the fetus and the mother, mostly at doses much higher than those commonly used in humans. Protracted parturition, maternal mortality, embryolethality, severe general underdevelopment and marked skeletal retardation of the fetuses (increased amount of diaphyseal bone trabeculae, decreased diaphyseal length), small fetal weight and abnormal tooth growth have been observed. DESIGN: We conducted a thorough research of the literature in order to identify human studies concerning this issue. RESULTS: We identified a total of 78 cases involving fetuses whose mothers had been exposed to BPs before conception or during pregnancy, along with 7 cases of BPs exposure prior to or during lactation. The vast majority of mothers and infants did not demonstrate serious adverse effects. However, there were cases of shortened gestational age, low neonatal birth weight and transient hypocalcaemia of the newborns, while the very few reported cases of spontaneous abortions and congenital anomalies probably resulted from maternal underlying diseases and concomitant medication. CONCLUSION: The administration of bisphosphonates in pregnancy should be assessed in view of their potential hazardous effects on both mother and fetus. In cases of absolute or relative indications of BPs prior to pregnancy, close observation of the mother and the infant, especially during the first two weeks of life, is imperative for the successful outcome of pregnancy.

Key words: Bisphosphonates, Lactation, Pregnancy

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INTRODUCTION

Bisphosphonates (BPs) are the most common drugs used for the treatment of osteoporosis, with more than 29 million prescriptions issued during 2006 in the USA.[1] BPs are also administered, with excellent results, in patients with hypercalcaemia, metastatic

bone disease (e.g. due to breast, lung, prostate cancer and multiple myeloma) and Paget disease, while BP treatment in other conditions characterized by high bone turnover such as osteogenesis imperfecta and fibrous dysplasia has been shown to reduce skeletal morbidity.[2] Nevertheless, although the vast majority of patients treated with BPs are postmenopausal women, the plethora of indications for BPs use has resulted in an increasing number of children, men and premenopausal women being treated with them.

Animal studies have demonstrated that BPs given to pregnant rats cross the placenta and result in reduced bone growth and fetal weight.[3] Furthermore, high-dose (up to 10 to 15 mg/kg/day), long-term BP administration to pregnant rats and rabbits shows significant maternal and offspring toxicity, mainly due to protracted parturition and hypocalcaemia in dams, this susceptible to prevention by concomitant intravenous calcium supplementation.[4] Moreover, BP administration at doses 10 times higher than human therapeutic doses resulted in embryolethality or severe underdevelopment and marked skeletal retardation.[5] These facts along with BPs long-term skeletal retention have given rise to serious considerations about the safety of BPs use in women of reproductive age due to the possible adverse effects on an eventual pregnancy (synchronous with or subsequent to treatment).

With the aim of recapitulating the knowledge acquired so far regarding the administration of BPs prior to or during pregnancy and lactation, we conducted a thorough research of the literature in order to identify reports concerning this issue.

METHODS

We performed our research through PubMed using the words "bisphosphonates" and "pregnancy" or "bisphosphonates" and "lactation" as key words. The initial number of articles that matched our criteria was 120. After the exclusion of those concerning animal or laboratory studies, reviews not adding new cases, cases with no exposure of the fetus or the infant to BPs and those where the fetus or the infant was exposed to BPs but not providing information about the outcome, the number of articles was reduced to 18.

We also searched the published trials of BPs administered for the prevention and treatment of glucocorticoid induced osteoporosis, Paget's disease and premenopausal osteoporosis. In these publications there was no report of BPs exposure during pregnancy and/or lactation. We did not include oncology patients in trials investigating the effect of BPs, such as zoledronate or pamidronate, on disease-associated events. However, we included single case reports of women with malignancy-associated hypercalcaemia due to breast cancer diagnosed during pregnancy and treated with BPs.

RESULTS

Seventy-eight cases of fetuses whose mothers had been exposed to BPs before conception or during pregnancy were identified, along with 7 cases of BPs exposure prior to or during lactation (Table 1). Alendronate p.o. and i.v. pamidronate were the commonest BPs used. Mean maternal age at conception was 32.2 years. Duration of BPs use prior to pregnancy ranged from 5 years to only 6 months. However, in 59 cases duration of prior BP exposure was not reported. In most cases treatment was stopped 3 months prior to or at conception, although there were at least 33 cases that received BPs during the first 3 months of pregnancy. Only a small number of women received BPs after the first trimester, mainly due to malignancy associated hypercalcaemia. Indications for BP administration included glucocorticoid-induced osteoporosis, pregnancy-associated osteoporosis, autoimmune diseases, osteogenesis imperfecta and polyostotic fibrous dysplasia and malignancy-associated hypercalcaemia. Mean gestational age was 36.5 weeks and mean birth weight was ~2.7 kg. Sixty-nine pregnancies resulted in live births, while 9 abortions (8 spontaneous, 1 voluntary) were noted; all of these abortions were attributed to maternal concomitant diseases and medication.

a. BPs prior to or during pregnancy

- Large case-series

The largest case-series study to date of pregnant women exposed to BP was reported by Ornoy et al. They studied the outcome of pregnancy in 24 women who were exposed to alendronate before conception or during the first months of pregnancy. These women were suffering from osteoporosis secondary

Table 1. Reported cases of BPs' use prior to and/or during pregnancy/lactation

Study	No. of pregnancies	Mean age at conception	BP	Dose	Duration of BP treatment	Administration conception	Indication	Concomitant treatments	Live births	Spontaneous abortions	Voluntary abortions	Median gestational age (ws)	Median birth weight (g)	Congenital malformation	Adverse infant outcome	Breast feeding	Adverse infant outcome during breast-feeding
Ornoy et al[6]	24	NR	alendronate	NR	NR	0-6 ms before (8), 0-8 ws during (15), 0-21 ws during (1)	ARD(13), OP(5), other (6)	CS (13)	19 (79.1%)	5 (20,8)	0	38	2910	0	NR	NR	-
Levy et al[7]	21	32.4	alendronate (12), etidronate (5), risedronate (2), pamidronate (2)	NR	NR	0-3 ms during (15), 3ms before (6)	CS induced OP (15), OP (5), metastatic cancer (1)	CS (15), AZA+SFZ (17)	18 (85.7%)	2 (9.5%)	1 (4.8%)	38.7	3100	1 (Apert syndrome)	2 (1premature birth, 1 jaundice)	NR	-
Losada et al[8]	10	35	alendronate, pamidronate, clodronate, neridronate	NR	NR	before or during	CS induced OP (7), primary OP (1), pelvic fracture (1), femoral avascular necrosis (1)	AZA(2), SFZ (1), CS(2), cyclosporine (1), hydroxychloroquine (1)	9 (90%)	1 (10%)	0	38	2890	2 [ventricular septal defect (clodronate), 1 kidney & cardiac malformation (alendronate)]	2 (1 premature birth, 1 distress syndrome)	NR	-
Chan et al[9]	4	29.5	pamidronate	iv 1mg/kg for 3 ds/4-6 ms	46ms	3ms before	McCune-Albright	no	4 (100%)	0	0	38	2500	0	0	Yes (18 ms)	0
					26ms	3ms before						Full term (>37)	NR			Yes	0
						48ms before						Full-term (>37)	NR			Yes	0
					iv 1mg/kg/2ms	19ms	21ms before	OI type IV					34	2270			Yes (6 ws)	0

d(s): days; w(s): weeks; m(s): months; y(s): year(s); Ref: Reference; BP: biphosphonate; prg: pregnancy; NR: not reported; iv: intravenous; p.os.: orally; OP: osteoporosis; ARD: autoimmune rheumatic disease; OI: osteogenesis imperfecta; PLOP: pregnancy/lactation associated osteoporosis; CS: corticosteroids; AZA: azathioprine; SFZ: sulfasalazine; CH: chemotherapy.

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Munns et al[10]	2	17.4	pamidronate	iv 1mg for 3 ds/4 ms	5 ys	Until prg	OI type I / OI type IV	no	2 (100%)	0	0	38	3230	1 (Bilateral talipes equinovarus)	1 (Transient hypocalcaemia)	NR	-
Hassen-Zrour et al[11]	1	30	alendronate / pamidronate	p.os. 10 mg/d / iv 90 mg/4 ms	6 ms / 1y	Before conception	OI type I	NR	1 (100%)	0	0	39	4000	0	0	Yes (3 ms)	1 [Transient hypocalcemia (2 ms of age)]
Harsch et al[12]	1 (triple)	30	alendronate	NR	3 ys	Until prg	PLOP	no	3 (100%)	0	0	NR	NR	0	0	NR	-
Athimulam et al[13]	1 (twin)	34	alendronate	NR	NR	Until prg	PLOP	no	2 (100%)	0	0	36	NR	0	0	NR	-
Vujasinovic-Stupar et al[14]	2	33 / 35	etidronate	p.os. 400mg/d for 14d/3m	1.5ys / 3.5ys	3m before / 3m before	PLOP	calcitonin	2 (100%)	0	0	Full term (>37) / Full term (>37)	NR / NR	0	0	NR	-
Cabar et al[15]	1	30	pamidronate	iv 1mg for 3 ds/4ms	3.5 ys	1m before	idiopathic hyperphosphatasia	no	1 (100%)	0	0	36	3130	0	0	NR	-
Rutgers-Verhage et al[16]	1	49	alendronate	p.os. 0.12 mg/kg/d	NR	Until prg	presumed postmenopausal OP	NR	1 (100%)	0	0	36	2390	0	1 [at one y of age weighed 8 kg (10th centile)]	NR	-
Mastaglia et al[17]	1	21	pamidronate	iv 60 mg/3 ms	1 y	3 infusions before & 1 during first trimester	Gaucher's disease type 1	intermittent enzyme replacement therapy	1 (100%)	0	0	37	2230	0	0	Yes (12 ms)	0

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Biswas et al[18]	2	NR	alendronate	NR	NR	First trimester (1), 2 ms before (1)	NR	NR	2 (100%)	0	0	NR	NR	0	0	NR	-
Dunlop et al[19]	1	28	aminopropylidene BP	iv 30 mg	once	34th gestational w		CH + CS	1 (100%)	0	0	36	3060	0	1 (transient hypocalcemia)	no	-
Illidge et al[20]	1	42	pamidronate	iv NR	once	28th gestational w	Malignant hypercalcaemia	Morphine + CS	1 (100%)	0	0	29	1412	0	1 (transient hypocalcemia)	no	-
Andreadis et al[21]	1	34	zolendronic acid	iv 4 mg/28 ds	-	2nd and 3rd trimester	(Metastatic breast cancer)	CH + Radiotherapy (28Gy) + tamoxifen	1 (100%)	0	0	35	2070	0	0	no	-
Culbert et al[22]	1	40	pamidronate	iv NR	once	28th gestational w		CH	1 (100%)	0	0	NR	NR	0	0	no	-
Simonski et al[23]	1	39	pamidronate	iv 30 mg/m	6 ms	Lactation period	Reflex sympathetic dystrophy	no	1 (100%)	0	0	40	NR	-	-	Yes (6 ms)	0
Total fetuses exposed in utero	78	32.2							69 (88.5%)	8 (10.8%)	1 (1.4%)	36.5	2707				
Total breast-fed infants	7																6.1 ms

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to major chronic disease and/or the medication against it. The diagnoses of the patients were as follows: systemic lupus erythematosus (SLE) (n=5), familial osteoporosis (n=4), Takayasu arteritis (n=2), Adamantiadis-Behcet's disease (n=2), hypothyroidism (n=2), rheumatoid arthritis (n=1), psoriatic arthritis (n=1), Crohn's disease (n=1), asthma (n=1), berylliosis (n=1), autoimmune hepatitis (n=1), early menopause (n=1), Laron syndrome (n=1), leprosy with perinatal listeria infection (n=1). The investigators found significantly lower median gestational age and birth weight compared to the control group, while the rate of spontaneous abortions was higher. However, these findings may be related to the maternal diseases responsible for osteoporosis or to the additional drugs taken, especially glucocorticoids. Among the offspring, no major congenital anomalies were observed.[6]

Levy et al performed a multicenter prospective cohort study including 21 women exposed to BPs during pregnancy or even 12 months before conception, due to primary or secondary osteoporosis, and 21 matched controls. Fifteen patients in the BPs group had first-trimester exposure and 6 patients discontinued the bisphosphonates within 3 months prior to conception, but further information about time of exposure was not reported. BPs used were as follows: alendronate (n=12), etidronate (n=5), risedronate (n=2) and pamidronate (n=2). The indica-

tions were primary osteoporosis (n=5), osteoporosis associated with cancer (n=1) and osteoporosis secondary to corticosteroid use, such as inflammatory bowel disease and SLE (n=15). Seventeen patients were on other medications during pregnancy because of these medical conditions, including azathioprine and sulfasalazine. The study's primary endpoint was neonatal outcome including major birth defects, while the secondary was the outcome of pregnancy (live births, spontaneous abortions, therapeutic abortions). There were no significant differences between the two groups in any outcome. One child, whose mother discontinued etidronate 3 months before conception, was born with Apert syndrome, an autosomal dominant acrocephalosyndactyly. However, it was not related to the medication as a linked gene mutation was found.[7]

Moreover, a recent review, that includes the aforementioned cohorts, adds data of 10 more women (mean age at conception 35 yrs/range 30-43 yrs) exposed to BPs (alendronate, pamidronate, clodronate, neridronate) before or during pregnancy. The indications for BP included corticosteroid induced osteoporosis in 7 cases, primary osteoporosis in 1, pelvic fracture in 1 and femoral avascular necrosis in 1. Other concomitant treatments were: azathioprine in 2 cases, sulfasalazine in 1, corticosteroids in 2, cyclosporine in 1 and hydroxychloroquine in 1. There was 1 spontaneous abortion and 9 newborns of mean gestational age 38 weeks and mean birth weight 2890g. Two congenital malformations, 1 ventricular septal defect (exposed to clodronic acid) and 1 kidney and cardiac malformation (exposed to alendronate), 1 premature birth and 1 distress syndrome were reported.[8]

- Cases of women treated with BPs due to osteogenesis imperfecta (OI) or polyostotic fibrous dysplasia (PFD)

Chan et al presented 4 infant outcomes of pregnancies of 3 women who were treated with intravenous pamidronate for 19-46 months before conception, 2 due to PFD, at a dose of 3 mg/kg every 4 months and 1 due to OI, at a dose of 1 mg/kg every 2 months. All of them had stopped medication for at least 3 months before conception. There were no pregnancy-related complications nor biochemical or skeletal abnormalities among the offspring.[9]

Another report of 2 cases dealt with the pregnancies of 2 women with OI, types I and IV, who received intravenous pamidronate for 5 years before conception. The first conceived at the age of 17 years and then discontinued pamidronate, which she had been receiving at a dose of 1 mg/kg on each of 3 consecutive days every 4 months since the age of 12. Throughout pregnancy she received daily 1000 mg calcium and 400 IU vitamin D. The woman delivered a boy of 3.6 kg at 37 weeks of gestation. The boy had hypocalcaemia at 24 hours of age, but phosphorus and iPTH concentrations were within normal range. On day 11 his calcium was normal. The boy inherited his mother's *COL1A1* mutation. The second woman, who had been receiving pamidronate from 12.5 to 17.8 years of age, conceived at the age of 17.8 years and delivered a girl of 2.86 kg at 38 weeks, who also inherited her mother's disease and presented bilateral talipes equinovarus. She had no signs or symptoms suggestive of hypocalcaemia. Both babies presented normal growth and no fracture throughout the next few months after birth.[10]

Recently, Hassen-Zrour et al reported the case of a 30-year-old woman with a 1-year history of diabetes mellitus and OI type I, who received bisphosphonates (10 mg alendronate qd for 6 months followed by 90 mg intravenous pamidronate every 4 months for 1 year) before conception. At 39 weeks of gestation she gave birth to a healthy female infant who weighed 4 kg and did not present any malformation or perinatal irritability due to hypocalcaemia. The baby was breastfed until she was 3 months old. The mother remained free of pain and fracture at 6 months postpartum. She did not exhibit bone loss during pregnancy and breast feeding.[11]

- Cases of women treated with BPs due to pregnancy-associated osteoporosis (PO) and various cases

A 30-year-old patient, suffering from osteoporosis since her first pregnancy and treated with alendronate, had a triple pregnancy 3 years later and stopped medication. The outcome of pregnancy was positive, though no further details were given about neonatal health.[12] Following that report, Athimulam et al[13] and Vujasinovic-Stupar et al[14] presented the outcome of 2 more cases of BPs-exposed women due to PO. In the first case,[13] a 34-year-old woman treated with

alendronate after her second delivery, discontinued BPs at the beginning of her third pregnancy. She had an uneventful pregnancy and delivered 2 healthy infants (the authors did not give information about duration of treatment, dose of alendronate and further follow-up of the newborns). Additionally, Vujasinovic-Stupar et al[14] reported the case of a woman treated with intermittent etidronate therapy (400 mg qd for 14 days every 3 months) due to PO beginning at the age of 30 years after her first pregnancy. At the age of 33 years and after being treated with etidronate for 1.5 years, she got pregnant for the second time. Her last cycle of etidronate was 3 months before conception, pregnancy and labor were uncomplicated and the baby (a full-term boy) was healthy at birth with no neonatal complications, no obvious skeletal deformities or hypocalcaemia and normal DXA values at follow-up. After the second delivery, the woman continued etidronate therapy for another 2 years and became pregnant again. Her last cycle of etidronate was 3 months before conception. Pregnancy and labor were uneventful. The baby (a full-term girl) was healthy at birth and follow-up.

In another report, a 30-year-old woman, who had been receiving intermittently intravenous pamidronate for 3.5 years (1 mg/kg for 3 consecutive days every 4 months) for the treatment of idiopathic hyperphosphatasia, got pregnant 1 month after the last administration. She gave birth to a healthy offspring at 36 weeks of gestation who did not present any clinical or biochemical abnormalities.[15]

An additional case report described a 49-year-old woman, amenorrheic for 2 years, who was receiving oral alendronate at a dose of 10 mg/day for postmenopausal osteoporosis. She was unaware of the pregnancy until delivery at 36 weeks of gestation. She delivered a girl, weighing 2390 g (50th centile), without obvious birth defects or laboratory abnormalities. At 1 year of age the infant's development was normal.[16] Recently, the case of a young woman diagnosed with type 1 Gaucher's disease on intermittent enzyme replacement and multiple vertebral fractures treated with intravenous pamidronate 60 mg every 3 months since the age of 20 was reported. While under treatment she became pregnant (total dose 240 mg - last during the first trimester). She delivered at the 37th week a healthy girl weighing 2230 gr by caesarean section

due to preeclampsia. Finally, an observational cohort study, conducted in the UK using the technique of prescription event monitoring and aiming to monitor the safety of alendronate, included the reports of 2 pregnancies. One patient took alendronate in the first trimester, while the other had stopped taking alendronate 2 months prior to conception. There were no problems reported during the pregnancies and both infants were healthy.[18]

- Cases of women treated with BPs due to malignancies

BPs are also commonly prescribed in the treatment of hypercalcaemia of malignancy. So far, 4 reports of pregnant women and furnishing information about the pregnancy outcome have been published. The first case concerned a 24-year-old woman who received 30 mg pamidronate at 34 weeks of gestation for malignant hypercalcaemia due to metastatic breast cancer. Two weeks later she gave birth to a healthy male child weighing 3.06 kg. The baby presented transient hypocalcaemia, with full recovery 5 days later. He had normal growth and development. Hypocalcaemia, apart from a direct effect of BP, could also be due to fetal parathyroid suppression by maternal hypercalcaemia.[19] Furthermore, another report of a woman with metastatic breast cancer in pregnancy treated with intravenous pamidronate at the 28th week of gestation documented no unfavourable impact on the fetus. Fetal calcium level was elevated at birth, subsequently dropped below normal and normalized 9 days after birth.[20] The third reported case was about a 33-year-old woman with metastatic bone disease due to breast cancer. She was not aware of her pregnancy until the 28th week. Zoledronic acid (4 mg intravenously every 28 days) was administered throughout the second and third trimesters. She gave birth to a normal female at 35 weeks of gestation which was followed up for 12 months and presented normal development.[21] The most recent report describes a 40-year-old multigravida woman diagnosed with metastatic breast cancer at 24 weeks of gestation and who received chemotherapy with unsatisfactory results. At 28 weeks she was given pamidronate for hypercalcaemia. Pamidronate successfully reduced maternal calcium levels and uterine contractions. The neonate presented normal serum calcium and iPTH levels.[22]

b. BPs and lactation

One report concerning a 39-year-old woman suffering from sympathetic dystrophy dealt with this issue. Intravenous pamidronate (30 mg) was administered at monthly intervals and breast milk was pumped and collected for 48 hours after the infusion. She resumed breastfeeding between pamidronate administrations. Pamidronate was quantified by high performance liquid chromatography (HPLC) with a limit of quantitation of 0.4 μmol/l. Pamidronate levels were below detection limits for all samples of milk tested. The baby remained healthy and presented normal growth.[23] In addition, in the case of the patient suffering from Gaucher's disease mentioned above, breastfeeding for 1 year was not accompanied by adverse effects to the infant's health and developmental rate.[17] In the report of 4 cases by Chan et al, also described above, women received intravenous pamidronate for 19-46 months before conception and all of them breastfed their babies for 6 weeks to 18 months. The infants remained healthy and no adverse events occurred.[9] The only adverse infant outcome reported during breastfeeding was transient hypocalcaemia. Specifically, the mother received BPs before conception and the neonate was breastfed for 3 months. At 2 months, investigation of the child revealed asymptomatic hypocalcaemia (2.10 mmol/l, normal range 2.25–2.65). At 5 months of age, normal serum calcium levels and normal long-bone X-ray were documented.[11]

c. Bone scintigraghy during pregnancy using BPs chemically attached by radionuclides

Although the main issue concerning bone scintigraghy during pregnancy is fetal radiation exposure, there is also concern regarding fetal skeleton uptake of BPs, which are used as the vehicle of the radionuclides. Existing data show different results when bone scan is performed at different stages of gestation. Two pregnant women underwent bone scintigraghy with technetium-99m methylene diphosphonate at 8 or 18 weeks of gestation. Although placenta exhibited marked uptake, fetal uptake was not demonstrated, while, notably, absorbed dose by fetuses was lower than maternal background levels in both cases.[24] In addition, another report presenting a 21-year-old woman, who also underwent bone scan following the same radionuclide injection at 16 weeks of gestation, suggests that there is no fetal uptake.[25] However, a report on the cases of 2 pregnant women with malignant tumors showed direct skeletal fetal and placental uptake of radionuclide at 30 and 32 weeks of gestation. None of the children presented adverse effects.[26] When a scan is required for pregnant women, the lowest dose for adequate results should be used.

DISCUSSION

Our research identified 78 cases of fetuses whose mothers had been exposed to BPs prior to or during pregnancy, with 69 live births. None of the newborns presented serious adverse events caused by BPs. The abortions that occurred were attributed to maternal concomitant diseases and medications.

Concern about BP use in women of childbearing age is related to the increased calcium requirements during pregnancy and lactation, the pharmacokinetic and pharmacodynamic properties of BPs that result in prolonged retention in the skeleton and suppression of bone turnover as well as animal data pointing to transplacental passage of BP and significant maternal and offspring toxicity, albeit at much higher doses compared to those approved in humans.

Gestation is a period with enhanced metabolic requirements for the pregnant woman and her skeleton, predominantly during the third trimester in which calcium is released from the mother's bones to fulfill the increased fetal demands (which are mainly satisfied by increased maternal intestinal calcium absorption).[27] In the event that the pregnant woman is treated with BPs shortly before conception or during gestation, suppression of bone turnover may result in fetal hypocalcaemia with detrimental consequences to its bone modeling and other cellular procedures in which calcium plays a dominant role.[28]

BPs' similarity to pyrophosphate accounts for their ability to bind with bone hydroxyapatite. Subsequently, they are taken up by osteoclasts where they exert their antiresorptive action. In a recent study by Nancollas et al, the most popular BPs were ranked according to their binding affinities for hydroxyapatite as follows: zoledronate > alendronate > ibandronate > risedronate > etidronate > clodronate.[29] Furthermore, the accepted comparative potency of BPs to inhibit osteoclast action is: zoledronate > risedronate > ibandronate > alendronate > pamidronate.[30] Oral

BPs have extremely low bioavailability and only about 1% of the administered oral dose is absorbed by the gastrointestinal tract. Of the absorbed amount, ~50% is distributed to bones, with the remainder quickly excreted (within hours) by the kidneys (<0.5% of the oral dose is excreted through bile).[31] However, the total elimination of BPs from the body is not accomplished via this initial renal excretion but is a multiphasic and long-term procedure owing to their prolonged binding ("burial") to bones (Figure 1).[32,33]

The above factors explain why BPs have long half-lives in the human body in contrast to their relatively short plasma half-lives. Since the mid-1990's, it has been known that after a single intravenous dose of alendronate in postmenopausal women with osteoporosis, who had never been treated with BPs, the estimated skeletal half-life of the BP exceeds 10 years (based on the data from the first 8 to 18 months' follow-up).[34] Additionally, the observation that pamidronate can be detected in urine of young patients up to 8 years after discontinuation of oral treatment is suggestive of BPs' long-term retention in the skeleton.[35] Moreover, a recent study evaluating urinary excretion of alendronate and risedronate in postmenopausal women previously treated with these drugs found that alendronate could be detected up to 19 months after drug cessation: urinary levels were inversely related to time of treatment discontinuation and directly related to uNTx levels. However, 5 months after treatment cessation risedronate was not detected, this underlining the known differences of these two commonly used BPs.[36] Finally, the fact that biochemical markers of bone turnover do not increase immediately and that the rate of bone loss is slow after cessation of treatment with these drugs, by contrast with hormone replacement therapy in postmenopausal women, is also indicative of BPs' retention in bones.[37-41]

In addition, BPs' small molecular weight possibly allows their passage through placenta and, eventually, some action on the fetus. Apart from animal studies, there are reports in the literature of 2 women who underwent bone scintigraghy with ^{99m}Tc-methylene diphosphonate while being in late gestation (>30 weeks).[26] In both cases there was radionuclide uptake from both the placenta and the fetus. Generally, placental permeability increases gradually throughout
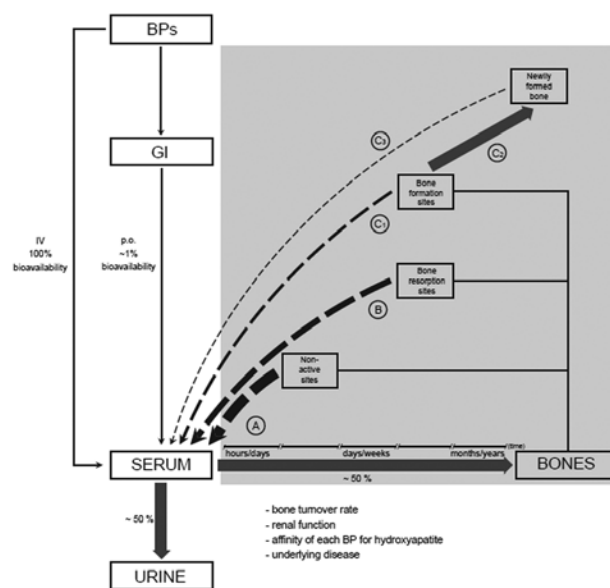

Figure 1. Schematic illustration of BPs' pharmacokinetics. Only ~1% of the administered oral dose is absorbed by the gastrointestinal tract (GI) and becomes bioavailable; when administered intravenously the bioavailability is 100%. Of the absorbed amount, ~50% is distributed to bones, while the remainder is excreted quickly (within hours) by the kidneys.[31] The amount of BPs taken up by the bones depends on the affinity of each BP for hydroxyapatite, the rate of bone turnover (which, in turn, is affected by a variety of factors, such as the underlying disease, age, etc.) and renal function.[32] The fate of BPs that reach the skeleton depends on the specific binding bone site. **A)** At non-active (resting) sites (~85% of all surfaces in a certain trabecular segment), BPs are bonded loosely, in small quantities, and return to blood circulation within hours/days, while a very small amount is retained/in bones.[33] **B)** At sites of bone resorption (~2% of all surfaces in a certain trabecular segment), which have about 8 times greater affinity for BPs than resting sites, the majority of the BPs returns to the blood circulation like non-active sites, but in this case the return lasts longer (days/weeks).[33] **C)** Finally, at sites of bone formation (~12% of all surfaces of a certain trabecular segment), which have about 4 times higher affinity for BPs than non-active sites, although a significant amount returns to blood within days/weeks (C1), mineralization with the calcium-BPs complexes leads to the incorporation of BPs into the newly generated bone (C2) and their long-term retention in an inert (as far as the bone turnover is concerned) condition, until a new circle of bone resorption liberates them and make them available (C3), either for reuse in bones or for excretion by the kidneys.[33] This "burial" of BPs is completed within hours/days, but the time these agents remain in this condition cannot be estimated precisely (it may last for years), since it depends on many factors, with bone turnover rate being the most important.

pregnancy, reaching maximum at around the 32nd week.[42] Thus, the aforementioned cases should not be extrapolated to BPs' use at earlier stages of gestation. They are however indicative of BPs' passage through placenta. BPs are potentially capable of directly disturbing bone modeling by acting on bone cells or indirectly through hypocalcaemia. Furthermore, recent data have shown an inhibitory effect of BPs on angiogenesis, thus an analogous harmful action is also possible on the fetus.[33]

The above issues highlight the complexity and the difficulty in handling women of reproductive potential needing BP treatment. Judging by the published cases, it seems that BP administration at the approved doses even during the first trimester of pregnancy does not result in significant toxicity. Even in the limited number of cases of malignancy-associated hypercalcaemia, intravenous BP use did not lead to significant infant or neonatal morbidity. Moreover, in cases of OI and PFD, extremely high dose BP treatment did not result in infant harm, apart from transient, reversible or easily treated hypocalcaemia. Thus, it seems that animal data, where the doses used were 10 to 100 times higher than the approved human (alendronate: 10 mg/kg/day in rats compared to 0.15 mg/kg/day based on a patient weight of 70 kg), do not apply in humans.

The lack of adequate data and the deficient quality of the published studies have led the US Food & Drug Administration to place most of the BPs in class C, i.e. animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Taking all the above into account, it can be concluded that BP treatment during pregnancy will probably result in fetal exposure. On the other hand, human data do not indicate significant toxicity even in women treated in late gestation, thus termination of pregnancy should most likely not be advocated. Moreover, in women of reproductive potential and with short-term increased fracture risk, such as temporary glucocorticoid treatment, it might be sensible to use BPs with low skeletal retention, such as rise-dronate, balancing it against the relative antifracture efficacy.[43] However, in cases of high fracture risk, such as OI or PFD, we advocate intravenous BPs administration to attain maximal suppression of high bone turnover in order to protect the maternal skeleton and reduce BPs recycling.

CONCLUSIONS

The safety of BP use by women of reproductive age has not as yet been fully established. There is evidence that BPs cross the placenta. When the administration of BP concerns women of childbearing age, their long-lasting retention and slow release back to systemic circulation might lead to exposure of the fetus. Animal studies have shown adverse effects both on the fetus and the mother, mostly at doses much higher than those commonly used in humans. Protracted parturition, maternal mortality, embryolethality, severe general underdevelopment and marked skeletal retardation of the fetuses (increased amount of diaphyseal bone trabeculae, decreased diaphyseal length), small fetal weight and abnormal tooth growth have been observed. Conversely, human reports regarding women exposed to BPs before conception or during pregnancy did not demonstrate serious adverse effects either to fetuses or to the mothers. However, there are cases of shortened gestational age, low neonatal birth weight and transient hypocalcaemia. While most authors warn against BPs administration prior to or during gestation, this recommendation is hard to apply in clinical practice. Some suggest that women treated with BPs and who are planning pregnancy should withhold medication for at least 1 year.[44] Our policy is to withhold medication for at least 6 months, especially in cases of high fracture risk such as OI or PFD. In these patients we advocate intravenous BPs administration to attain maximal suppression of high bone turnover in order to protect maternal skeleton and reduce BPs recycling. Thus, each case should be managed taking into account the risk/benefit balance. Nevertheless, monitoring serum calcium levels during pregnancy and lactation and during the first weeks of the infant's life is imperative for the successful outcome of pregnancy.

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