Toxicological risk of magnesium alloys as implant materials – theoretical and experimental assessment

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ABSTRACT INTRODUCTION:

Current metallic implants are relatively strong, but they are not absorbable, and might cause side effects if left inside the body in the long term. Current degradable implants are relatively week. Resorbable magnesium implant is unique that it has both advantages, combining the better mechanical strength and the ability to be fully absorbed by the body. However, despite the obvious advantage, investigations were not very popular, and there were many aspects that were not yet explored.

Although risk assessment is a gold standard in the public health perspective, to the best of our knowledge it was never conducted on this class of biomaterial by other groups. Dose-response assessment, as a standard step in risk assessment, was conducted hereby to provide a quantitative theoretical estimation of the tolerable amounts of common magnesium alloys and other resorbable metallic materials. A relevant animal assessment was conducted to verify the theoretical estimation.

METHODS – THEORETICAL ASSESSMENT

Common magnesium alloys AZ91D, AM50A, AM60B and pure magnesium were selected for the assessment, and ASTM upper limits of component element abundance were utilized[1]. Toxicological information on critical studies of oral exposure limits were obtained from US Agency for Toxic Substances and Disease Registry (ATSDR)[2], and US EPA Integrated Risk Information System (IRIS)[3]. The assessment was modified from a WHO model[4].

Uncertainty factors (UFs) adopted were the same as those selected by ATSDR and IRIS whenever possible. However, no extra uncertainty or modifying factor would be used if the primary data was already an RfD (reference dose), as interspecies and human variability had already been considered when deriving RfD. Gastrointestinal absorption efficiencies of elements were obtained from ATSDR and UK Food Standards Agency, for adjusting the data to account for 100% absorption.

The TE-aa was then multiplied by 60kg and 365 days, to generate an element-specific reference annual exposure, which is the tolerable annual exposure of a specific element for a healthy 60kg individual according to the NOAEL value. 12 months was arbitrarily chosen as the length of time for full degradation of a non-permanent implant in small orthopedic applications, being long enough for the required function without causing excessive disturbance or long-term effects to the patient.

Relevant computations were expressed by the following equations:

Equation 1 Raw Tolerable Exposure (TE-r) in mg/kg/day
= (NOAEL equivalent) / (interspecies UF) / (interindividual UF)
Equation 2 Absorption-adjusted Tolerable Exposure (TE-aa)
= TE-r x absorption efficiency from oral route
Equation 3 Reference annual exposure (RAE) to a 60kg adult (in mg/yr)
= TE-aa x 60 x 365 = 21900 x TE-aa

To determine the annual guidance exposure of an alloy, the element-specific RAE of each element in an alloy was then divided by its maximum abundance in the alloy. The resultant reference value, now defined as Abundance-Adjusted Reference Annual Exposure (AARAE), would be equal to the component-specific threshold alloy mass when this component element was assumed the sole source of adverse effects.
Equation 4 Abundance-Adjusted Reference Annual Exposure (AARAE)
= RAE / abundance of the specific component element

The lowest AARAE among component elements for a given alloy would then indicate the lowest alloy mass sufficient to produce an adverse effect, as an implant to be completely absorbed in 12 months.

Equations 1 to 4 may also be rearranged into one single equation:

Equation 5 AARAE (in mg/yr) = threshold implant mass

$$= \frac{\text{(NOAEL equivalent x oral absorption efficiency) x 21900}}{\text{(UF x abundance)}}$$

METHOD – EXPERIMENTAL ASSESSMENT

Animal ethics approval was obtained. Rod of 4mm wide, 10mm long were alkali-treated and immersed in DMEM to deposit a protective layer, then implanted subcutaneously at the back of each mouse. Six mice of ~30g weight were used for each implant group. Animal behavior was monitored, and implants were retrieved at 6 months for compression test.

RESULTS

Theoretical assessment Threshold masses and volumes of Mg-based implants according to the dose-response assessment are tabulated below:

	Al	Mn	Zn
Critical value (mg/kg/day)	26	0.14	0.83
Data source	ATSDR: Chronic animal NOAEL	IRIS: Chronic human NOAEL	ATSDR: Intermediate human NOAEL
Absorption efficiency	0.63%	5%	20%
Uncertainty factor	100 (ATSDR)	1 (IRIS)	3 (ATSDR)
$RAE_{60kg\ human}$ (mg/year)	35.9	153.3	1211.8
AZ91D			
ASTM max. abundance[1]	9.7%	0.5%	1.0%
AARAE (gram/year)	0.37	30.6	121.2
Threshold mass for human	0.37gram/yr		
Equivalent mass for 30g mouse	0.19mg/yr		
AM50A			
ASTM max. abundance[1]	5.4%	0.6%	0.22%
AARAE (gram/year)	0.66	25.6	550.8
Threshold mass for human	0.66gram/yr		
Equivalent mass for 30g mouse	0.33mg/yr		
AM60B			
ASTM max. abundance[1]	6.5%	0.6%	0.22%
AARAE (gram/year)	0.55	25.6	550.8
Threshold mass for human	0.55gram/yr		
Equivalent mass for 30g mouse	0.28mg/yr		

Experimental assessment No fatality could be linked to the implants. Minor side effect of diarrhea was observed in low frequency. Forelimb grip force was reduced but it could be correlated with the anesthesia. Other measurable side effects were not observed. Non-toxicological data are discussed elsewhere. **Note:** Threshold implant masses for 60kg human were divided by 2000 to derive the data for 30g mice. Approx. mass of implanted rod = 3.14 x $(0.2)^2$ x 1800mg/cm^3 = 226mg.

DISCUSSION

Although the resorbable Mg-based implants might theoretically be sufficient to cause toxicological side effects in human, such side effects (except diarrhea) were not observed in the animal model. One important reason was that in accordance with common practice [2,3,4], uncertainty factors were applied in the calculation to address interspecies and interindividual differences. Also, as the maximum abundances in the specifications were used in the theoretical assessment, it would likely be higher than the actual abundance. On the other hand, a lack of serious side effects may also be linked to the unexpectedly low rate of corrosion (10-16.8% reduction in ultimate compressive strength of the implants in 6 months), and presence of oxidized Al residue near the implantation site (Yuen and Ip, unpublished). Despite no severe harmful effects were observed, potential toxicological issue should not be overlooked. Further experiments are required to determine if the extended period of corrosion would cause prolonged, undesirable effects on issues. Larger populations are also required for a more thorough assessment.

REFERENCES

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