

Research letters

Totally implantable hearing device for sensorineural hearing loss

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Almost 15% of the adult population of western nations has sensorineural hearing loss.¹ Insufficient speech comprehension, acoustic distortion, and occlusion of the outer ear canal are disadvantages of conventional hearing devices. We report total implantation of a piezoelectric hearing system (figure).

If the ear is stimulated with an electromechanical transducer attached to a middle-ear ossicle, sound fidelity is greater than that achieved by stimulating the ear with a loudspeaker.^{1,2} A piezoelectric transducer has physiological displacement amplitudes of 70 nm from 50 Hz to 4 kHz and around 500 nm at 9 kHz. Nonlinear distortions are small (0.5%) throughout the frequency range. Low energy consumption allows the use of an implantable battery that is recharged by a portable inductive charging unit. We constructed an implantable broadband microphone³ for the reception of sound and an implantable 3-channel audioprocessor which can be digitally programmed by induction. Experiments on animals models showed that the cochlea could be stimulated to a reliable degree if the transducer was coupled to an ossicle.⁴

The device was implanted into one ear of five patients (two women) with bilateral sensorineural hearing loss. The microphone, weight 0.4 g, is housed in a sealed titanium capsule, and has a membrane 4.5 mm in diameter. It was implanted subcutaneously in the dorsal wall of the bony outer ear canal near the tympanic membrane. The audioprocessor and battery, inside a flat titanium and ceramic housing, was implanted subcutaneously behind the ear in a cavity of the skull made by removing the tabula externa. The transducer,

0.4 g in weight, made of titanium and also hermetically sealed, was implanted into the mastoid and coupled to the body of the incus with an Erbium-YAG laser.

3 to 12 weeks after surgery, all patients could hear without distortion and with high sound fidelity. Pure-tone audiograms showed threshold gains up to 40 dB above 2 kHz. The implant led to a gain in speech intelligibility of 20–60% and auditory localisation by 20–32%. In all patients, the area of surgery healed well and there was no visible sign of surgery apart from the retroauricular scar.

The study was done according to the rules of the Declaration of Helsinki and according to the Good Medical Practice (GMP) and approved by the University of Tübingen Ethics Committee. All patients had given their informed consent to both study and publication. We thank Marcus M Maassen, Rolf Lehner, Peter Plinkert, Rainer Zimmermann, Gabriele Reischl, and Joachim Baumann. We also thank Anthony Gummer for critical review of the manuscript.

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Fatal interaction between ritonavir and MDMA

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Information on drug interactions between prescribed drugs is generally available, but interactions between prescribed medication and illicit drugs are more anecdotal and seldom reported. We report on a fatal interaction between ritonavir and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy").

A man born in June, 1964, tested HIV-1 positive in 1991, and developed AIDS in 1995. He had been a heavy alcohol drinker with strikingly abnormal liver function, and a fatty liver was seen on ultrasonography. He had decreased his alcohol intake to a few units per week from March, 1996, onwards, which led to improved liver function, but his aspartate transaminase remained raised at 173 IU/L (normal 11–55 IU/L). His treatment for AIDS was altered to add ritonavir 600 mg twice daily on Sept 20, 1996, to his regular medication of zidovudine 200 mg three times daily and lamivudine 150 mg twice daily. He had taken MDMA on several occasions without untoward effects, and had kept three tablets from his last supply of the drug. He went to a club on Oct 6, 1996, and took the tablets with him and was seen drinking beer. 4 h after arrival he was obviously unwell. When assessed by a nurse who was attending the club, he was hypertonic, sweating profusely, tachypnoeic



Radiograph of implant

(1) transducer, (2) coupling of transducer to incus, (3) microphone, (4) battery and audioprocessor.

(45 breaths/min), tachycardic (>140 beats/min), and cyanosed; his jugular venous pressure was not raised. He was able to talk in full sentences and gave a history of having taken two Ecstasy tablets with little effect, so he took a further half tablet, after which he began to feel shaky (estimated total dose 180 mg MDMA, calculated from the MDMA content of the remaining half tablet). Within 25 min of the first assessment he had an apparent tonic-clonic convulsion, but was able to respond to questions. He became increasingly tachypnoeic, and his carotid pulse rate was about 200 per min. A few minutes later he vomited and had a cardiorespiratory arrest. Attempts at resuscitation were unsuccessful.

At necropsy, the lungs were strikingly oedematous and congested, the liver showed some pallor and had a slightly fatty appearance, but there were no other significantly abnormal features. No tissue samples were retained for possible pharmacogenetic studies. Toxicology showed blood concentrations of MDMA 4.56 mg/L, 3,4-methylenedioxyamphetamine 0.36 mg/L, and ethanol of 0.24 g/L. No other illicit drugs were detected. Ritonavir concentrations were not measured.

MDMA has been previously associated with death, most commonly through excessive exertion leading to hyperthermia.¹ Cases of overdose have been described,¹ with ingestion of 42 tablets leading to an MDMA concentration of 7.72 mg/L, which caused mild systemic effects;² in another case, overdose of 18 tablets led to an MDMA concentration of 4.05 mg/L and life-threatening illness,³ with symptoms similar to our patient. The protease inhibitor, ritonavir, is a potential inhibitor of CYP2D6, an isozyme responsible for demethylation, the principal pathway by which MDMA is metabolised.^{3,4} Thus, ingestion of MDMA in recreational amounts by a person taking ritonavir could lead to toxic effects due to a high plasma concentration of MDMA, which the results suggested had happened in our patient. A plasma concentration of about 0.5 mg/L of MDMA would be expected after ingestion of 180 mg, but the actual concentration was almost ten times that anticipated. In addition to a possible drug interaction, the patient's metabolism of MDMA may have been poor; 3–10% of white people are deficient in CYP2D6.⁵

Impaired hepatic function may have decreased the biotransformation of MDMA. Death was consistent with a severe serotonergic reaction to MDMA. Severe reactions to MDMA need, therefore, to be identified immediately and urgent transfer to hospital arranged. Samples should be taken for possible pharmacogenetic analysis.

Ritonavir could interact with many drugs that are metabolised by CYP2D6, including amphetamine derivatives. The potential for interactions of prescribed medications with MDMA should be highlighted. Manufacturers' instructions should contain the appropriate warnings of the danger of interactions with illicit drugs.

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Reporting of safety data from randomised trials

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Randomised trials estimate the efficacy and toxicity of interventions. While the quality of efficacy reporting in such trials has drawn a lot of attention,^{1,2} the reporting of safety data has not. We evaluated systematically the quality and extent of information on drug toxicity in reports of randomised trials. We selected treatments for HIV-1 infection, where drug toxicity is common and drugs are mostly new, and so safety should be a priority. All published randomised trials, 1987–97, with sample size of 100 patients or more (n=60; enrolment 36 280) were assessed with prespecified quality measures.

Although most trials (81.7%) reported how many patients discontinued study treatment, reasons were given in only 38.3%. The severity of adverse events and abnormal laboratory tests was adequately defined only in 33.3% and 61.7% of reports, and partially defined in a further 20% and 13.3%. Estimates were closely replicated by a second independent rater (kappa coefficients 0.72 and 0.85 for clinical and laboratory measures, respectively). Adequate definition was specified as detailed description of severity; or reference to known toxicity scales with reporting of severe and higher-grade event frequencies per arm for at least two side-effects. Partial definition meant that the report did not separate moderate from severe or higher toxicity; or, severe and higher grade event frequencies were given only for one of many reported side-effects. Protocols with inadequate definitions lumped numbers for all grades; did not split numbers per arm; gave no numbers for any specific events; provided only generic statements ("the medication was overall quite well tolerated"); or did not report on safety. Nine trials gave no frequencies for any clinical adverse events and 11 trials gave no frequencies for any laboratory toxicity.

No table was used for safety data in 19 reports (31.3%), while there was no figure with such data in 52 (86.3%). Considering text, tables, and figures together, the median percentage of space allocated to safety information in the results section was 13% (interquartile range, 7–19%). The median space allocated to safety results was 0.5 page (mean 0.54 page), marginally smaller (p=0.056) than the space

Predictors	Absolute space pages (p)		Relative space %* (p)	
	Univariate	Multivariate	Univariate	Multivariate
Double blind	0.09 (0.55) NS		-0.3 (0.93) NS	
Dose comparison involved	0.18 (0.14) NS		7.7 (0.01) NS	
Dose comparisons only	0.31 (0.07)	0.46 (0.01)	17 (<0.001)	17 (<0.001)
Significant efficacy endpoint	0.02 (0.88) NS		-2.4 (0.36) NS	
Mainly government funding	0.06 (0.58) NS		2.3 (0.37) NS	
High citation journal†	-0.05 (0.67) NS		-2.5 (0.34) NS	
Long-term trial (>1 year)	-0.04 (0.71) NS		-0.4 (0.88) NS	
Other results space (per page)	0.06 (0.22)	0.12 (0.02)	NP	NS
Paediatric study	0.06 (0.73) NS		5.3 (0.22) NS	
Prior indication	-0.26 (0.07)	-0.26 (0.06)	-5.0 (0.14) NS	
Sample size (per 1000)	-0.04 (0.66) NS		-2.4 (0.26) NS	
Conducted in USA	0.17 (0.13) NS		4.6 (0.09) NS	
Year (per 10 years)	-0.17 (0.27)	-0.54 (0.01)	-3.5 (0.56) NS	
First trial of N≥100	0.21 (0.06)	0.23 (0.02)	3.7 (0.16)	4.7 (0.04)
Constant		0.45 (0.01)‡		11 (<0.001)‡

Negative coefficients mean that absolute space or percentage is reduced in presence of predictor. NS=not significant; variable not selected in backward elimination model based on likelihood ratio test with p>0.10 for removal and p<0.05 for entry. NP=not pertinent in the regression for percentage of space. *The space allocated to safety divided by the total space of the results section. †Journal citation impact factor above 7. ‡Constant referring to year 1987.

Regression analyses for space allocated to safety information in results section