study using pulse-mode ultrasound at 36 kHz for five minutes in a step procedure of increasing dosage, from 1.57 to 3.50 W/cm^2, and placebo in 34 healthy volunteers (79). The primary outcome was toxic effects of the procedure, defined as a pain score >40 on a 0- to 100-mm visual analogue scale or necrosis. Erythema (scored from 0 to 3 in severity) was also evaluated. We found no pain score >38 and no skin necrosis with either ultrasound or placebo. Erythema was systematically observed immediately after ultrasound exposure, but after 1 day, we observed only three cases. The most frequent adverse effect was tinnitus.

43.6 STABILITY OF DRUGS EXPOSED TO ULTRASOUND

Possible degradation of drugs due to ultrasound has been checked *in vitro* using ultrasound at high intensity, and no degradation occurred with poly l-lysine (31), insulin (8), fentanyl, or caffeine (30). Persistent *in vivo* biological activity of insulin and low-molecular-weight heparin is also in accordance with the absence of significant degradation in the conditions used (7–9).

43.7 PROSPECTS: IS PAINLESS NEEDLE-FREE INJECTION A REALISTIC GOAL?

There is no doubt that ultrasound can markedly increase transdermal transport *in vitro* and *in vivo* in animals and humans (1, 6–13, 60, 62, 78, 80, 81). Findings published between 1990 and 2010 were encouraging, especially for diabetes therapy, as it was possible to decrease glucose blood levels in animals *in vivo* (6, 7) and monitor it using inverse sonophoresis (35). The daily dose of insulin required to treat an adult diabetic patient is usually between 30 and 60 IU, and the amount delivered to animals is about 0.5 to 1 IU for a short period. Thus repeated pulses over the day would theoretically make possible the administration of a daily dose. However, 19 years after Mitragotri's first paper, no ultrasound device is used to deliver insulin in humans perhaps because (1) human barrier skin is more difficult to overcome with ultrasound than animal skin, (2) sonicating 1 cm^2 of a rat weighing 500 g is expected to be much more effective than sonicating 1 cm^2 of a 60-kg human, and (3) there are technology problems to proposing a small ultrasound device powerful enough to deliver the ultrasound intensity necessary to achieve drug delivery. Other problems include short- and long-term safety in humans, reproducibility, standardization of the process, extension of sonicated area, and cost. Thus there is no doubt that further studies are required (81).

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