bisphosphonate via an acetic-acid linker. The biodistribution characteristics and elimination rate from bone of DIC–BP were then examined by *in-vivo* studies with Sprague-Dawley rats. The skeletal distribution of DIC–BP was extrapolated from the amount detected in the femur, in proportion to the femur's contribution to total skeleton weight.

Rats received DIC–BP intravenously at doses of 0.32, 1.0, 3.2 and 10.0 mg kg^{-1}. At an appropriate time after administration, blood samples were collected. After the last sampling, the rats were sacrificed, and the brain, lungs, heart, kidneys, liver, spleen and femur were excised and assayed to determine drug concentration. At all doses, the amount of DIC–BP remaining in plasma was <2% of the dose when tissue samples were collected. DIC–BP was detected in the femur, liver and spleen, but the concentrations of DIC–BP in the brain, heart, lungs and kidneys were under the limit of detection. DIC–BP was taken up into the skeleton at all doses but tended to increase as a fraction of dose with increasing dose. The amounts of DIC–BP recovered in the skeleton were: 57.9 ± 13.0, 54.1 ± 3.3, 38.3 ± 6.4 and 24.8 ± 1.4% of administered dose at 0.32, 1.0, 3.2 and 10.0 mg kg^{-1}, respectively. The liver was another target for the accumulation of DIC–BP; the amounts recovered in the liver were 21.8 ± 1.1, 18.3 ± 0.7, 23.5 ± 2.3 and 38.9 ± 1.2% of the administered dose at doses of 0.32, 1.0, 3.2 and 10 mg kg^{-1}, respectively. Thus, the liver was the major target-organ for the disposition of DIC–BP at a dose of 10 mg kg^{-1}. The investigators believe that this effect is closely related to the propensity of bisphosphonate drugs to precipitate with metal ions (i.e. iron and calcium), and that this can be controlled by maintaining a low dose to avoid the precipitation effects.

For the determination of elimination rate from bone, a separate group of rats received a 10 mg kg^{-1} intravenous dose of DIC–BP. After an appropriate time (up to 28 days) post-injection, blood samples were collected, the animal was sacrificed, and the femur was excised. DIC–BP was detected in the femur over the entire 28 days of the experiment. The peak localization of DIC–BP was observed within 8 h after dosing. After 8 h, the skeletal concentration of DIC–BP declined in a biphasic manner with half-lives of 3.8 days in the early phase (from 8 h to 2 days) and 9.7 days in the terminal phase (from 4 to 28 days). Sustained release of regenerated DIC into the bone compartment was observed over the entire experimental period, and the bone concentration of regenerated DIC was constant throughout the 28 days.

Finally, the therapeutic and side effects of DIC–BP were compared with those of DIC in an adjuvant-induced arthritic rat model. DIC-sodium salt was administered daily by the oral route and DIC-BP was administered weekly by the intravenous route. For both DIC and DIC–BP, inhibitory effects against the swelling of rat paws were observed after a dose of 0.32 mg kg^{-1}, and arthritic scores detected in rat paws and tail were improved after a dose of 3.2 mg kg^{-1}. Both effects increased in a dose-dependent manner. Taking into account the frequency of medication (17 doses for DIC–sodium and four doses for DIC–BP in the experimental period), ED_{50} values of DIC and DIC-BP were corrected to 9.4 and 5.2 mg kg^{-1} (per experimental period), respectively. DIC treatment caused GI damage, even at the lowest dose of 0.032 mg kg^{-1}, with mean ulceration doses of 0.8 and 3.7 mg kg^{-1} for stomach and intestine, respectively. DIC–BP showed an improved side-effect profile: neither stomach nor intestinal ulcers were observed in rats treated with DIC–BP. These early studies did not address an oral formulation of DIC–BP, but it is significant that the sustained release of DIC into bone from DIC–BP permitted effective once weekly intravenous dosing. The bone-specific delivery and sustained release properties of DIC-BP could enhance the pharmacological effects of DIC for bone disease, while simultaneously preventing adverse GI effects and increasing patient compliance by a decrease in the frequency of administration.

1 Hirabayashi, H. *et al.* (2001) Bone-specific delivery and sustained release of diclofenac, a non-steroidal anti-inflammatory drug, via bisphosphonic prodrug based on the Osteotropic Drug Delivery System (ODDS). *J. Control. Release* 70, 183–191

John Weidner
Scientist, Parallel Synthesis
Medicinal Chemistry
Emisphere Technologies
765 Old Saw Mill River Rd
Tarrytown, NY 10591, USA
tel: +1 914 785 4792
fax: +1 914 593 8250
e-mail: Jweidner@emisphere.com

Erratum

Please note a correction to 'Current progress on new therapies for Alzheimer's disease' by Patrick C. May published in *Drug Discovery Today* 6(9), 459–462. On page 461, first column, the last two lines should have read 'Oral administration of one of the BMS inhibitors, dose undefined...'

The Editorial team of *Drug Discovery Today* would like to apologize for this inaccuracy and for any confusion that we might have caused.