

# Early Postconcussion Return to Play Discouraged

BY DOUG BRUNK

SAN DIEGO — No junior high or high school athlete who sustains a concussion in contact sports should be allowed to return to play that same day, because on average, simple concussions have recognizable deficits 8 days after the injury, according to Dr. Suraj Achar.

Concussion “is a serious brain injury that has been underrecognized and un-

dertreated,” Dr. Achar said at a meeting sponsored by Rady Children’s Hospital and the American Academy of Pediatrics. “Parents, coaches, trainers, and doctors should resist the temptation to let the kids go back on the field.”

In 2008, the National Football League mandated that team physicians forbid players to resume the game on the day of a concussive injury, and Dr. Achar believes a similar standard of care is ap-

propriate for young athletes.

In football, an estimated 10% of college players and 20% of high school players in the United States sustain concussive injuries each season (JAMA 1999;282:958-63), yet about 80% of cases are never reported, either because they are missed by nonmedically trained observers or because the athlete resists being pulled onto the sidelines and may not recognize the seriousness of what

happened, explained Dr. Achar of the department of sports medicine at the University of California, San Diego.

He noted that younger children are more susceptible to concussions, compared with their older counterparts, for reasons that remain unclear. Yet maybe one in four concussions have long-term manifestations. Single concussions may lead to changes in mental and physical functioning for 30-plus years, Dr. Achar said.

A widely used diagnostic instrument is the standardized assessment of concussion (SAC) system, which tabulates a summary of total scores in orientation, immediate memory, concentration, delayed recall, strength and coordination, and exertional maneuvers. An athlete who scores even 1 point less than the optimal 30 points is considered to have suffered a concussion.



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A study of male college and high school athletes found that the SAC had sensitivity of 94% and a specificity of 76% (J. Intl. Neuropsychol. Soc. 2001;7:693-702). Neuroimaging tests usually are not ordered after a concussion because the results tend to be normal. Deficits generally are functional, not structural, said Dr. Achar, who practices family and sports medicine in La Jolla, Calif.

A consensus paper on concussion in sport, classified concussions as either simple—meaning that symptoms resolve in 7-10 days with no obvious sequelae, no intervention is required, and neurologic testing is negative—or complex, meaning that symptoms persist after 7 days and worsen with exertion, prolonged loss of consciousness and cognitive impairment occur, and the patient has a history of multiple concussive injuries (Br. J. Sports Med. 2005;39:196-204). “You need a multidisciplinary team to care for these patients,” said Dr. Achar, who had no potential conflicts of interest to disclose.

In minors, “concussive symptoms can last up to 3 weeks. With sophisticated computer testing, neurologic deficits rarely resolve before 8 days after the injury. We want to completely rest them.”

The path for return to play begins with light aerobic exercise, followed gradually by sport-specific exercises such as skating in hockey or running in soccer, with progressive addition of resistance training. Finally, noncontact training drills and full-contact training drills may be resumed, and the athlete may return to play after medical clearance.

If any postconcussive symptoms occur, the consensus guidelines recommend that the patient drop back to the previous asymptomatic level and try to progress again after 24 hours. ■

Table 2 (continued): Incidence (%) Of Treatment-Emergent Adverse Reactions In Placebo-Controlled, Add-On Studies In Adults Experiencing Partial Onset Seizures By Body System (Adverse Reactions Occurred In At Least 1% Of Immediate-Release KEPPRA-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

| Body System/<br>Adverse Reaction | Immediate-Release<br>KEPPRA<br>(N=769)<br>% | Placebo<br>(N=439)<br>% |
|----------------------------------|---------------------------------------------|-------------------------|
| Hostility                        | 2                                           | 1                       |
| Paresthesia                      | 2                                           | 1                       |
| Emotional Lability               | 2                                           | 0                       |
| Respiratory System               |                                             |                         |
| Pharyngitis                      | 6                                           | 4                       |
| Rhinitis                         | 4                                           | 3                       |
| Cough Increased                  | 2                                           | 1                       |
| Sinusitis                        | 2                                           | 1                       |
| Special Senses                   |                                             |                         |
| Diplopia                         | 2                                           | 1                       |

In addition, the following adverse reactions were seen in other well-controlled studies of immediate-release KEPPRA tablets: balance disorder, disturbance in attention, eczema, hyperkinesia, memory impairment, myalgia, personality disorders, pruritus, and vision blurred.

**Postmarketing Experience** In addition to the adverse reactions listed above for immediate-release KEPPRA tablets [see *Adverse Reactions, Clinical Studies Experience*], the following adverse events have been identified during postapproval use of immediate-release KEPPRA tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The listing is alphabetized: abnormal liver function test, hepatic failure, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), suicidal behavior (including completed suicide), thrombocytopenia and weight loss. Alopecia has been reported with immediate-release KEPPRA use; recovery was observed in majority of cases where immediate-release KEPPRA was discontinued.

DRUG INTERACTIONS

**General Information** *In vitro* data on metabolic interactions indicate that KEPPRA XR is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C<sub>max</sub> levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, valproate, oral contraceptive, digoxin, warfarin, probenecid) and through pharmacokinetic screening with immediate-release KEPPRA tablets in the placebo-controlled clinical studies in epilepsy patients. The following are the results of these studies. The potential for drug interactions for KEPPRA XR is expected to be essentially the same as that with immediate-release KEPPRA tablets.

**Phenytoin** Immediate-release KEPPRA tablets (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

**Valproate** Immediate-release KEPPRA tablets (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

**Other Antiepileptic Drugs** Potential drug interactions between immediate-release KEPPRA tablets and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

**Oral Contraceptives** Immediate-release KEPPRA tablets (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

**Digoxin** Immediate-release KEPPRA tablets (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

**References:** 1. Brodie MJ, Kwan P. Staged approach to epilepsy management. *Neurology*. 2002;58(suppl 5):S2-S8. 2. Buck D, Jacoby A, Baker GA, Chadwick DW. Factors influencing compliance with antiepileptic drug regimes. *Seizure*. 1997;6:87-93. 3. Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. *Epilepsy Behav*. 2002;3:338-342. 4. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA*. 1989;261:3273-3277.

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