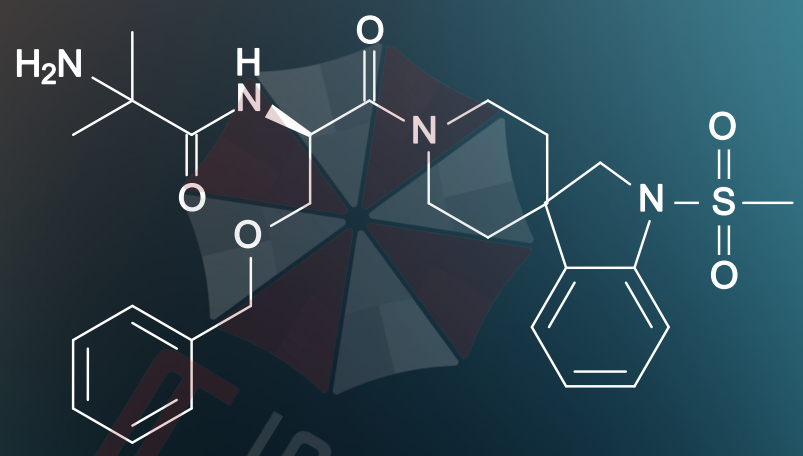

MK-677 in Clinical Research: Analyzing Its Promise and Limitations

MK-677, also known as Ibutamoren, MK-0677, L163,191 or LUM-201 is a synthetic analog of the endogenous hormone ghrelin. Ghrelin is short for growth hormone releasing inducing, hence, MK-677 is also able to induce the release of human growth hormone hGH (or somatotropin). Effects of growth hormone on the tissues of the body can generally be described as anabolic. It induces the growth of muscle mass and the synthesis of new muscle protein, increases the burning of fat and stimulates the immune system, besides an number of other metabolic effects. Since MK-677 releases hGH, its effects on the human body are mostly comparable to those of hGH. MK-677 was first reported in 1995 by Merck.[1]

MK-677 can be taken by mouth and currently holds the title of a new investigational drug in the united states. It is also included in the prohibited list of the World Anti- Doping Agency. However, it has been used experimentally by some in the bodybuilding community.

The synthesis of the compound has been described in a publication from 1998[2], and new routes have been published at a later time.[3],[4]

Detection

As MK-677 is monitored in anti-doping tests, one study reported the detection of MK- 677 via HPLC at very low concentrations in the picogram range from blood samples.[5],[6]

Animal Experiments

Along with the first published study about MK-677, data on beagle dogs has been released, showing a clear increase in GHRH (a precursor of hGH) in the dogs blood minutes after the administration of the drug.[1] Later experiments on the compound in mice confirmed an increased expression of GHRH in the brains of mice after injections of MK-677.[7]

Clinical Studies

Obesity is associated with blunted GH secretion, unfavorable body composition, and increased cardiovascular mortality. The objective of a clinical study on 24 healthy obese subjects was to investigate the impact of oral MK-677 treatment on GH secretion and body composition. Serum insulin-like growth factor I (IGF-I) increased approximately 40% with MK-677 treatment. hGH and prolactin (PRL) were significantly increased after the initial dose of MK-677. The increases in GH and PRL after the initial dose were significantly greater than the increase seen after multiple

doses. Fat-free mass increased significantly in the MK-677 treatment group. However, fat mass did not significantly change during treatment. Fasting concentrations of glucose and insulin were unchanged, whereas an oral glucose tolerance test showed impairment of glucose homeostasis at 2 and 8 weeks. The authors concluded that further studies are needed to evaluate whether a higher dose of MK-677 or a more prolonged treatment period can promote a reduction in body fat.[8] The fact that fat mass is not affected by MK-677 administration did surprise the authors, since it is known that hGH decreases fat mass. In theory, MK-677 should have the same effect. Another clinical trial sought to find the reason for this finding and discovered secondary effects of MK-677 on other metabolic markers such as thyroid hormones and the hormone leptin.[9]

Idiopathic Pediatric Growth Hormone Deficiency (iPGHD) results in a shortness of stature in children because hGH is also responsible for growth of the skeleton. MK- 677 was successfully used in two studies to stimulate growth in children with iPGHD. Two groups with a dosing of 1.6 and 3.2 mg/kg/day were tested. Growth was essentially the same in both groups and MK-677 was well tolerated. No safety concerns were identified across the dose range in adverse events.[10,11]

Growth hormone (GH) also stimulates bone mineralization and growth. Probably a major effect of GH on bone is mediated through stimulation of either circulating or locally produced insulin-like growth factor I (IGF-I). The authors of another study determined the effect of chronic administration of MK-677 on serum IGF-I and markers of bone turnover in 187 elderly adults lasting 2–9 weeks. Treatment with 10 mg and 25 mg of MK-677 for 2 weeks increased markers for bone growth in the blood of the patients. Additionally, MK-677 increased serum IGF-I levels significantly (55–94%).[12] Another clinical trial in obese young men found similar results.[13]

A follow-up trial on 292 postmenopausal women (64–85 years) with low bone density were randomly assigned in a 3:3:1:1 ratio to 1 of 4 daily treatment groups for 12 months: 25 mg MK-677 plus 10 mg alendronate (a drug known to inhibit bone breakdown); 10 mg alendronate; 25 mg MK-677 (25 mg); or placebo. MK-677, with or without alendronate, increased insulin-like growth factor I levels from baseline ~ 39% and 45% vs. placebo. MK-677 and alendronate mitigated the reduction in bone formation compared with alendronate alone. GH-mediated side effects were noted in the groups receiving MK-677, although adverse events resulting in discontinuation from the study were relatively infrequent.[14]

A defining feature of MK-677 is the increased muscle growth directly induced by the compound, which may be used in the elderly who are suffering from sarcopenia or in young people who choose a vegetarian or vegan lifestyle and do not consume enough protein to sustain muscle mass. In one small experimental study, 8 healthy volunteers (ages 24–39) were calorically restricted (18 kcal/kg·day) for two 14-day periods. During the last 7 days of each diet period, subjects received either oral MK- 677 25 mg or placebo once daily. MK-677 (25 mg) was generally well tolerated and without clinically significant adverse effects. MK-677 reverses diet-induced loss of nitrogen (marker of muscle breakdown), suggesting short-term anabolic effects are maintained in patients who are catabolic because of certain acute or chronic disease states, and it may be useful in treating catabolic conditions.[15]

Aging is associated with declining activity of hGH, possibly contributing to body composition changes and increased incidence of cardiovascular disease. 32 healthy subjects (aged 64-81) were enrolled in a randomized trial and received placebo or 2, 10, or 25 mg MK-677, orally. At baseline and on day 14 of each study period, blood was collected every 20 minutes for 24h to measure hGH, prolactin, and cortisol. MK-677 administration for 2 weeks increased hGH concentrations in a dose-dependent manner, with 25 mg/day increasing mean 24-h GH concentration 97 %. With 25 mg/day MK-677 treatment, mean serum IGF-I concentrations increased into the normal range for young adults. MK-677 also produced significant increases in

fasting glucose. Circulating cortisol concentrations did not change, and prolactin concentrations increased 23%, but remained within the normal range.[16]

In male individuals, 5 and 25 mg MK-677 had a significant impact on sleep. This was shown by a study in old and young men, who participated in two 14-day treatment periods with MK-677 (with bedtime drug administration). Doses were 2 and 25 mg MK-677. In younger subjects, high-dose MK-677 treatment resulted in an approximately 50% increase in the duration of deep sleep and in a more than 20% increase in REM sleep as compared to placebo. The frequency of deviations from normal sleep decreased from 42% under placebo to 8% under high-dose MK-677. In older adults, treatment with MK-677 was associated with a nearly 50% increase in REM sleep. This suggests that MK-677 can improve sleep quality and correct the sleeping irregularities associated with old age.[17]

In healthy young men, a small study over 7 days found an increase in IGF and associated proteins as well as an increased frequency of hGH secretion from the pituitary gland. Only small changes in serum cortisol levels were observed during this study. Body composition was not investigated during this short-term study.[18]

Interestingly, in obese men, a study found that MK-677 (25 mg/day) did influence blood lipid levels in the short term, but not in the long term. The changes were seen after 2 weeks, but at 8 weeks most parameters had returned to pre-study levels.[19]

Another study focused on neurological effects of MK-677, was conducted in which 563 patients with mild to moderate Alzheimer's disease were randomized to receive MK-677 25 mg or placebo daily for 12 months. Administration of MK-677 25 mg resulted in a 60.1% increase in serum IGF-1 levels at 6 weeks and a 72.9% increase at 12 months. However, there were no statistically significant effects on the symptoms or progression of Alzheimer's disease.[20]

Conclusion

MK-677 has been investigated in numerous clinical studies in the past 20 years and has shown interesting properties. Taken together, the amount of available data is very good and the multitude of studies claiming similar results suggest good reliability of the data published so far. MK-677 primary effects are an increase in lean body mass and bone density as well as improved sleep quality, although it has been investigated in a variety of other conditions.

Typical clinical dosing is 25 mg/day for adults, taken by mouth. At this dose, minimal adverse effects have been reported. Detailed reports on toxicity and maximum safe dosage were not available. However, based on the mode of action of MK-677, increasing the dose over 25 mg/day, even significantly, should not lead acute toxic effects. However, some studies have shown that increasing the dose does not lead to a stronger effect, hence there seems to be no practical benefit to increase the dose over the benchmark of 25 mg/day.

Some studies show MK-677 does increase insulin resistance, which may complicate its application in diabetic individuals or lead to a manifestation of diabetes of pre-diabetic patients.

Additionally, one clinical study on the impact of MK-677 on Nonalcoholic Fatty Liver Disease is being performed at the present time. (NCT05364684)

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