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CURRENT DEVELOPMENTS REGARDING GHB AND GBL INCIDENTS, TREATMENT AND DETECTION: A QUALITATIVE REVIEW

Aron T. E. Veerman and *Selene R. T. Veerman

S.R.T. Veerman, MD, PhD, Mental Health Service Noord-Holland Noord, Community Mental Health Division, Oude Hoeverweg 10, 1816 BT Alkmaar, The Netherlands.

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***Corresponding Author**
Dr. Selene R. T. Veerman
S.R.T. Veerman, MD, PhD, Mental Health Service Noord-Holland Noord, Community Mental Health Division, Oude Hoeverweg 10, 1816 BT Alkmaar, The Netherlands.

ABSTRACT

In this qualitative review we address the neuropharmacological properties of gamma-hydroxybutyric acid (GHB) and its precursor gamma-butyrolactone (GBL), which explain why these drugs are highly addictive, and cause serious symptoms of intoxication and withdrawal. In various countries the medicinal use of the sodium salt of GHB is approved for narcolepsy, cataplexy, treatment of opioid and alcohol withdrawal, and sedation as an anaesthetic. The abuse of illicit GHB and GHB-related drug incidents have increased in the past decade in the Netherlands, other European countries, Australia, and the USA. Treatment of GHB and GBL intoxication involves appropriate supportive care and monitoring. A serious withdrawal syndrome can be prevented by titration tapering with pharmaceutical GHB. This alternative to benzodiazepines proves to be effective and safe, especially in patients who have developed resistance to benzodiazepines. At present, a high relapse rate remains a permanent complication. In addition, GHB is used in drug-facilitated sexual assault (DFSA). Boron-dipyrromethene (BODIPY) dyes are used as fluorescent sensors: GHB Orange for GHB detection and Green Date for GBL detection. We examine whether GHB Orange is a reliable, real-time detection test to prevent nonintentional ingestion of GHB. Our findings highlight the limitations of BODIPY dyes as drug detection tests. Finally, we conclude that the core of prevention of date rape remains education to increase public awareness of DFSA by both medical health professionals and parents.

KEYWORDS: Gamma-hydroxybutyric acid. Gamma-butyrolactone. Intoxication. Withdrawal. Date rape. Detection.

INTRODUCTION

Gamma-hydroxybutyric acid (GHB) was synthesized by Henry Laborit in 1961.[1] He was a French surgeon, who intended to create a gamma-aminobutyric acid (GABA) analogue that would cross the blood-brain barrier.[2] Due to the strong sedative properties GHB was considered a new and effective anaesthetic agent. After the discovery this anaesthetic and hypnotic agent was shortly available as Gamma-OH. Despite the relatively stable hemodynamic properties Gamma-OH became obsolete, because alternative anaesthetic agents were developed with less side effects, such as hypernatremia, nausea and vomiting.

GHB was launched as a nutritional supplement and in the eighties GHB became popular among bodybuilders, because it was hypothesized to stimulate the production of growth hormone, promoting muscle growth, and decreasing body fat.[3] Several medical indications for the use of GHB followed, such as obesity with accelerated fat burn, sleep disturbance with a prolonged effect on slow delta-wave sleep, depression with euphoria, alcohol withdrawal syndrome as antidote and sexual dysfunction with enhancement of sexual functioning through disinhibition.[2] Nowadays, the mode of action and metabolic effects of GHB are not yet fully understood. In contrast to the earlier hypothesis, GHB does not increase growth hormone, but has potentially anti-obesity properties due to central and peripheral metabolic effects.[3]

GHB was banned for sale as a supplement in the United States of America (USA) by the Food and Drug Administration (FDA) in 1990.[4] GHB is an illicit recreational drug and gamma-butyrolactone (GBL) is the precursor of GHB. GHB and GBL are dangerous substances, since these compounds are extremely addictive.[5] It seems that in the past decade the abuse of GHB and GBL has increased in the Netherlands, other European Countries, Australia and the USA.[6.7]

Based on alarming messages in social media, in newspapers and the news on radio and television, the prevalence of sexual abuse using drugs has increased as well. In order to prevent drug-facilitated sexual assault (DFSA), prevention guidelines and several real-time drug detections tests have been developed.[8,9]

In this qualitative review, we briefly address the neuropharmacological properties of GHB and its precursor GBL to understand the symptoms and treatment of GHB and GBL intoxication and withdrawal. We examine the recent developments regarding GHB related incidents, varying from abuse, intoxication, withdrawal, and sexual assault. We explain the

mechanism of action of two different boron dipyrromethene (BODIPY) dyes: Green Date for GBL detection and GHB Orange for GHB detection. We aim to explore whether these fluorescent sensors for GHB and GBL are reliable, real-time detection tests to prevent nonintentional ingestion of GHB. We replicate an experiment with GHB Orange and test its efficacy to detect GHB in several aqueous solutions, its specificity for GHB, and its pH sensitivity. Finally, we offer advice for the prevention of DFSA.

GHB NEUROPHARMACOLOGY

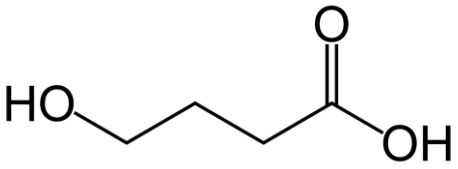

Fig. -1: GHB molecule ($C_4H_8O_3$).

GHB ($C_4H_8O_3$) is a lipophilic, short fatty acid and is therefore able to cross the blood-brain barrier (Fig. 1). GHB is a neuromodulator, which is naturally produced in the central nervous system of mammals.[10] GHB is closely related to the inhibitory neurotransmitter GABA, which promotes sleep and relaxation. GHB is metabolized to GABA. There are GHB receptors distributed throughout the human brain with the highest receptor density in the cortex, the hippocampus, the olfactory tracts and the cerebellum. GHB shows a high affinity to these specific GHB receptors, but also acts as a weak agonist of GABA-B receptors.[11,12] The physiological effect of GHB is dose dependent.[13] In small dosages GHB acts as an agonist at the excitatory GHB receptor, which explains the positive effect of GHB with euphoria, increased libido and sociability. In large dosages GHB acts at inhibitory GABA-B receptors, resulting in sedation, respiratory depression and hypotension.

GHB absorption, hepatic transformation as well as elimination are fast processes with a half-time of 30-50 minutes.[5] Therefore, GHB has a short effect. GHB is an attractive recreational drug, because of the lack of hangover effects.[14] Therefore, GHB is also known as ‘liquid G or liquid ecstasy’.

GHB can be easily produced adding potassium hydroxide (KOH) and warm distilled water to GBL.[2] The solution is slowly heated for an hour and vinegar is added until the pH is below 7.5. GHB is a solid and white compound. A salty or bitter taste can be a signal for the presence of GHB. Furthermore, GHB is colourless and odourless and has a high solubility in

aqueous solutions, which makes it difficult to detect in beverages. GHB consumption in the party scene is usually in mixtures with soft drinks, water or alcohol.

GBL NEUROPHARMACOLOGY

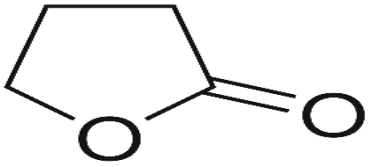

Figure -2: GBL molecule ($C_4H_6O_2$).

The limited availability of GHB due to more stringent regulations caused a shift to the chemical precursors GBL and 1.4-butanediol ($C_4H_{10}O_2$).[4] These compounds for the production of GHB can be easily obtained and are abundantly available. GBL is approved in the legitimate chemical industry.[15] GBL is available as a common solvent for several products, including nail polish remover. GBL is relatively easily acquired via the internet. Hence, GBL has become a more preferred date rape drug over GHB due to the less harsh legal status, the availability, and the low cost.

GBL ($C_4H_6O_2$) itself is pharmacologically inactive, but it is easily metabolized in the liver by lactonase to GHB (Fig. 2).[16] Therefore, GHB and GBL have similar neuropharmacological effects after ingestion. Since GBL is more lipophilic than GHB it is absorbed more rapidly upon oral administration, resulting in a higher bioavailability.[14] The elimination of GBL is very fast just like GHB.[17] GBL has similar chemical properties compared to GHB: it is colourless and odourless. Therefore, GBL is also not easily detected in beverages.[14]

MEDICINAL USE OF GHB

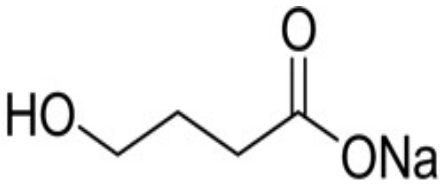

Figure -3: Sodium oxybate molecule ($C_4H_7NaO_3$).

At present, the sodium salt of GHB (Fig. 3) has medicinal use as anaesthetic Somsanit®, approved in Germany for the sedation of neonates and premature babies.[18] Sodium oxybate is also registered under the name of Alcover® for the treatment of opioid and alcohol withdrawal in Austria and Italy. A third medicinal use of sodium oxybate is Xyrem®,

approved in Canada for cataplexy and for narcolepsy with cataplexy in the USA and Europe. Sodium oxybate is a first-line option for narcolepsy and cataplexy. Narcolepsy is a rare neurological disorder which presents with a severe sleeping disorder, motoric, neuropsychiatric, and metabolic symptoms. Cataplexy is a sudden muscle paralysis triggered by strong and positive emotions.[20] Cataplexy is one of the major symptoms of narcolepsy. The knowledge on the neurobiology of emotions and motor control is limited. The combination of narcolepsy and cataplexy is commonly caused by an immune-mediated process, including genetic and environmental factors.[19] GABAergic neurons of the central nucleus of the amygdala are hypothesized to promote emotion-triggered cataplexy, since they target brain stem regions which regulate muscle tone.[20] Cataplexy is substantially increased by selective activation of GABAergic neurons in the central nucleus of the amygdala and inhibition of these GABAergic neurons reduces reward-promoted cataplexy.

Illicit GHB and the pharmaceutical product sodium oxybate differ in accessibility, purity, and dosing, as well as in the prevalence and potential consequences of misuse and abuse.[18] While sodium oxybate is manufactured and distributed under strict conditions that allow the prospective monitoring of potential cases of abuse and dependence, illicit GHB and especially GHB precursors such as GBL and 1.4-butanediol are more widely available. Furthermore, sodium oxybate is produced and stored according to Good Manufacturing Practice standards, while illicit GHB is synthesized and sold in a manner in which the purity and dose of the illicit formulation are often unknown to the consumer. Moreover, sodium oxybate is specifically prescribed to be taken in bed and not to be taken with alcohol or other central nervous system depressants, whereas illicit GHB is often consumed at frequent intervals and combined with alcohol or other illicit drugs.

GHB Abuse

It is difficult to assess the prevalence of GHB abuse. GHB abuse is more common among visitors of large parties and clubs. However, the abuse of GHB seems to have spread beyond the party scene. The number of GHB-related drug incidents in the Netherlands, other countries in Europe, Australia and the USA has increased steadily.[6,7] In the Netherlands, one in five drug incidents in ambulances concern GHB.

Ten thousands of people in the Netherlands use GHB on an annual basis. Some of these people are addicted to GHB. Most people who are addicted to GHB are ambivalent about kicking the habit, because of the positive effects of this drug. Symptoms of withdrawal are

extremely serious, which makes it complicated to stop. The number of GHB abusers who seek medical treatment has increased substantially.

A recent cohort-study using nationwide administrative data from regular Dutch Addiction Treatment Centres associated with the Dutch National Alcohol and Drugs Information System (LADIS) demonstrated high levels of treatment consumption and high rates of treatment re-enrolment in GHB-dependent patients. Currently, effective relapse prevention interventions for GHB-dependent patients are not available and these findings emphasize the need for the development of these measures.

GHB and GBL Intoxication

GHB intoxications are generally caused by non-medical use with illicit GHB or GBL. Patients with an intoxication are presented at medical emergency units with a coma of short duration and are often released from hospital a few hours after appropriate supportive care and monitoring.[21] Intoxication may lead to dangerously low respiratory rates, unconsciousness, seizures, and bradycardia. Because of the more lipophilic properties of GBL, the risk of intoxication is even higher compared to GHB.[14] When GHB or GBL are combined with alcohol, the consumption can be even more life threatening, because alcohol potentiates the effects of GHB intoxication and increases the inhibiting effects on the central nervous system, resulting in respiratory depression, hypotension and a decreased heart rate.[22]

GHB and GBL Withdrawal

Development of tolerance and dependence of GHB occurs when GHB is used regularly in a period of weeks.[21,6] GHB-dependent users take GHB every one or two hours to prevent withdrawal symptoms, even in the nighttime. A severe withdrawal syndrome is caused by sudden cessation or reduction of intensive GHB use. Symptoms of GHB withdrawal vary from tremor, anxiety, psychosis with hallucinations and delusions, delirium, agitation, insomnia to autonomic instability with tachycardia, seizures and rhabdomyolysis.[23,24,25,21,26,6] GHB withdrawal syndrome can even be life threatening. The first-choice treatment of the GHB withdrawal syndrome used to consist of supportive care and high doses of benzodiazepines. However, GHB and GBL users can develop resistance to benzodiazepines.[26] In the past decade the controlled detoxification of GHB using pharmaceutical GHB in an adjusted dose is investigated in the Netherlands. Detoxification by titration and tapering with pharmaceutical GHB seems to be an effective and safe alternative to benzodiazepines as a GHB detoxification procedure with hypertension

and anxiety as main complications.[27] However, high relapse rates warrant further investigation of this procedure.[23,27]

Date Rape

Drug-facilitated sexual assault (DFSA) is a criminal act, defined as the 'voluntary or involuntary ingestion of a drug by a victim that results in an act of sexual activity without consent'.[28] Date rape drugs include alcohol, GHB, GBL, flunitrazepam (rohypnol), and ketamine.[8] These substances are popular among perpetrators, because they act rapidly, cause inhibition and relaxation of voluntary muscles, and anterograde amnesia. Therefore, victims of sexual assault are not able to remember what occurs under the influence of these drugs.

Apart from alcohol, flunitrazepam, GHB and GBL are the most frequently used date rape drugs. A systematic review by Németh et al. (2010) on the relationship between GHB use and sexual abuse or unwanted sexual behaviour showed that the rate of GHB-positive samples among victims of reported sexual assault was between 0.2 and 4.4%.[29] However, the prevalence of GHB-related sexual assault is probably higher for several reasons. Firstly, although involuntary ingestion of drugs relieves victims of social judgement of culpability or responsibility, victims often do not report sexual assault due to the social stigma related to sexual assault. Secondly, due to the short half-time GHB is detectable in blood eight hours after ingestion and in urine after twelve hours. Examination of the victim often occurs after this period of time has passed by. To prove GHB administration, urine or blood samples should be collected as soon as possible, because of the rapid elimination of GHB.[17]

Education and guidance of adolescents and young adults by both health care professionals and parents is important to prevent DFSA. Many are unaware of the dangers of date rape drugs such as GHB, especially in combination with alcohol.[8,30]

Sensor for GBL

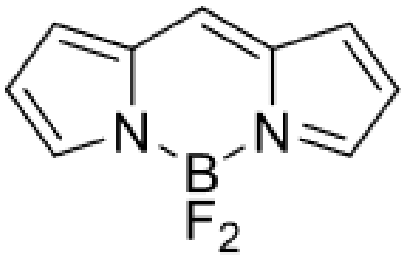

Figure - 4: Structure of a BODIPY molecule.

In the past few years, boron-dipyrromethene (BODIPY) derivates are used for fluorescence labelling and have been proven to be safe fluorescent sensors in biological and biomedical studies.[31] BODIPY dyes are used in bio-imaging with minimal systemic toxicity.[32] BODIPY dyes are excellent fluorescent markers for biomolecules, due to their outstanding photophysical properties and low cellular toxicities. Furthermore, the biological function of biomolecules is not significantly influenced when BODIPY derivates are attached, because of their small molecular size (Fig. 4). Fluorescent sensors are attractive tools as a real-time detection method because of their high sensitivity, fast response time, and technical simplicity.[32] BODIPY dyes are activated with on/off modulated fluorescence emission. These switching properties are linked to the photo induced electron transfer (PET) characteristics of the dimethyl amino functionalities, which are attached to the BODIPY core. Benefits of BODIPY dyes are the fast on/off emission and the fact that the PET reaction is reversible, both in solution and in vitro.

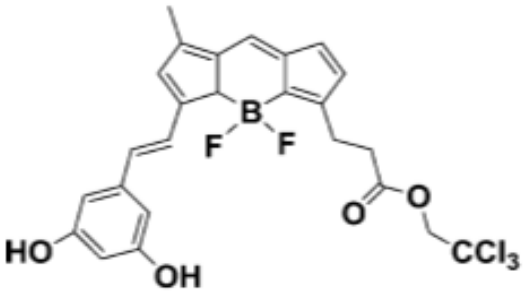

Figure -5: Structure of a Green Date molecule with two hydroxyl groups.

In the past decade, several drug detection kits have been developed for date rape drugs such as ketamine, flunitrazepam and GHB in order to prevent DFSA.[9] In 2013 the first fluorescent sensor for GBL was developed as a real-time detection method.[33] The hydroxyl groups play a prominent role in the interaction with GBL. The most effective BODIPY derivate is the 3,5-dihydroxyl compound with two hydroxyl groups (Fig. 5).

This sensor is called Green Date because it has an absorption and an emission maximum at 569 and 582 nm, respectively. The fluorescence intensity of Green Date and the concentration of GBL within a range of 0 to 100 mg per mL shows a linear relationship. The detection limit for GBL is reached at a concentration of 3 mg per mL. After a simple extraction method with dichloromethane ($C_2H_2Cl_2$) to remove interfering coloured components from beverages and concentrate GBL more than ten times its original concentration, Green Date has proven to be

a visual detection test for GBL in various drinks. The fluorescence intensity of Green Date varies in several beverages, both alcoholic, non-alcoholic, coloured and colourless drinks with and without GBL. Green Date proved to be efficacious as a detection test under both acidic and basic condition, since a consistent fluorescent response to GBL was demonstrated within the pH range of 2 to 11. Considering the fact that GBL is often mixed in alcoholic drinks, it is important that Green Date also has a fluorescent effect in combination with GBL and alcohol. After the extraction method, the presence of GBL can be simply visualized using ultraviolet (UV) light from a green laser pointer. While the green light of the laser can pass through a sample without GBL, an orange fluorescence is turned on when the sample contains GBL.

Both GBL and Green Date are relatively hydrophobic. Hydrophobic fluorescent molecules of Green Date stack together in polar solvents to minimize contact with water. The aggregated Green date molecules form dynamic particles, which results in diminished fluorescence. This mechanism is known as static quenching. When the GBL concentration increases at 300 mg mL^{-1}, the dynamic particles decrease in the solution and the static quenching effect of Green Date is reduced. As a result, the fluorescence of Green Date turns on.

In summary, Green Date is hydrophobic and forms non-emissive aggregates in water, which are broken by GBL.[9] After a simple extraction method with dichloromethane the presence of GBL can be determined by irradiation with a green laser, which induces the appearance of orange fluorescence. According to Zhai et al. (2013) Green Date is a reliable detector for GBL in alcoholic, non-alcoholic, coloured, and colourless beverages.

Sensor for GHB

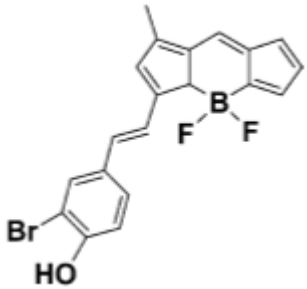

Figure -6: Structure of a GHB Orange molecule with a single hydroxyl group.

GHB Orange is a BODIPY dye with a single hydroxyl group in its structure (Fig. 6).[34] GHB Orange has an absorption and an emission maximum at 557 and 574 nm, respectively in a 50% ethanol aqueous solution. The name for this detection test is explained by the fact that

solutions which do not contain GHB have an orange colour under the irradiation of a hand-held 365 nm lamp. Zhai et al. (2014) proved GHB Orange to be an efficacious detection test for GHB. In various alcoholic, non-alcoholic, coloured and colourless beverages spiked with GHB an obvious fluorescence intensity decrease was observed by the naked eye. The fluorescence intensity fold change of GHB Orange showed a linear decrease with respect to the concentration of GHB within a range of 0 to 100 mg per mL. The fluorescence intensity differences between GHB-free and GHB-spiked beverages were observed under the irradiation of a hand-held 365 nm lamp. The differences were easily distinguishable by the naked eye within less than 30 seconds. GHB Orange showed a distinct fluorescence quenching response to GHB in alcoholic, non-alcoholic, coloured, and colourless beverages.

In January 2019, at the Science Faculty of the University of Amsterdam (UvA) we replicated this experiment with GHB Orange combined with water, cola, Crystal Clear and beer. We enhanced the solubility of the lipophilic BODIPY dye GHB Orange by a relatively large quantity of a highly polar organic solvent dimethyl sulfoxide (DMSO). We used both GHB and sodium acetate (CH_3COONa) to test whether GHB Orange is a specific drug test for GHB. We used sodium hydroxide (NaOH) and hydrochloric acid (HCl) to study whether this detection test is reversible.

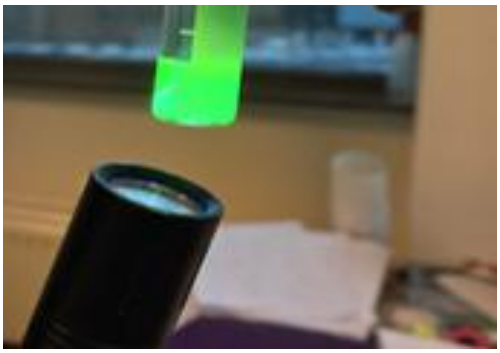

Figure -7: GHB Orange under exposure of UV lamp light (366 nm).

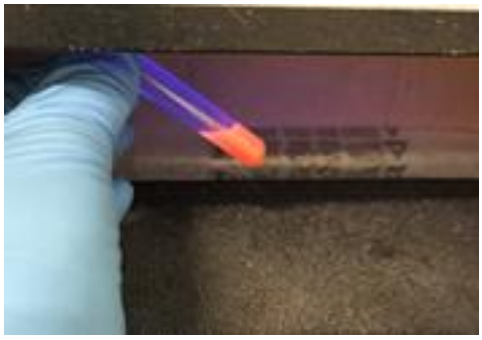

Figure -8: GHB Orange solved in DMSO irradiated by an UV light lamp (366 nm).

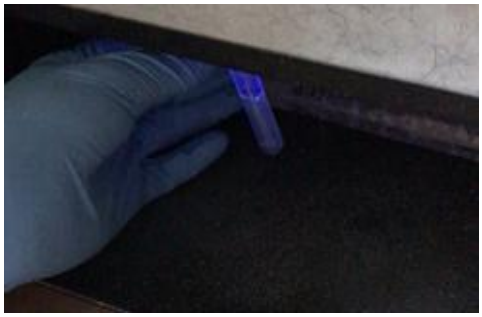

Figure -9: A solution of GHB Orange and DMSO combined with GHB under exposure of an UV lamp light (366 nm).

GHB Orange has a green colour, irradiated by an UV light lamp (Fig. 7). Firstly, we added 1 mg GHB Orange to 1.5 mL DMSO. Secondly, we added 1 drop (5 uL) of the solution GHB Orange and DMSO to 4 mL water, cola, Crystal Clear, and beer, respectively. However, the fluorescent effect did not appear. When 1 drop (5 uL) of the solution GHB Orange and DMSO was added to 4 mL DMSO the fluorescent effect appeared (Fig. 8), which was quenched after addition of GHB. The colour changed from fluorescent orange to dark green (Fig. 9). The same results were found for both GHB and sodium acetate. The fluorescent orange colour returned after addition of 1 mL sodium hydroxide and the colour turned to dark green again after addition of 1 mL hydrochloric acid.

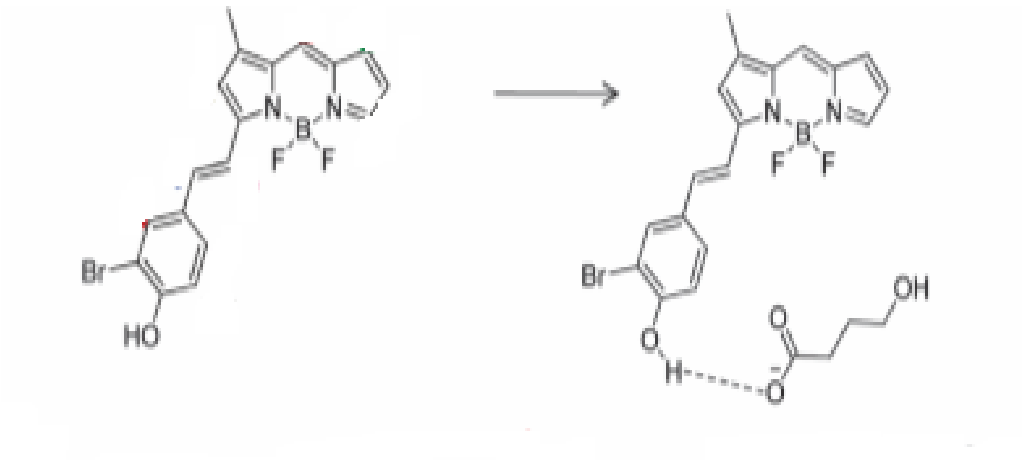

Figure 10: Mechanism of action of GHB Orange with the formation of a hydrogen bond between the hydroxyl group of GHB Orange and GHB.

The mechanism of action of this detection test is explained by the formation of a hydrogen bond between the phenolic hydrogen atom of the GHB Orange molecule and the carboxylate moiety of the GHB molecule (Fig. 10). Due to the formation of this hydrogen

bond, the electron intensity of GHB Orange increases. As a result, the photo-induced electron transfer (PET) effect enhances, quenching the fluorescence of GHB Orange. Hence, the reaction between GHB Orange and GHB activates a PET process, which induces an emission quenching. This process can be observed clearly by the naked eye under the irradiation of a hand-held 366 nm lamp.

In conclusion, under exposure of UV light GHB can be detected by the BODIPY dye GHB Orange. A PET process is activated, which induces an emission quenching, which can be observed clearly by the naked eye. The formation of hydrogen bonds seems to be limited when BODIPY is combined with aqueous solutions, such as water, cola, Crystal Clear and beer. This GHB detection test seems only effective in combination with a relatively large amount of DMSO, which enhances the solubility of the lipophilic BODIPY dye in aqueous solutions. It is also possible that the pH sensitivity of the BODIPY dye affects the fluorescent effect, which makes it difficult to find an effective sensor for all aqueous beverages. BODIPY can also be used as a pH indicator since an alkaline solution has an orange fluorescent colour under UV light irradiation and the colour turns green in an acidic solution. This colour change is reversible.

DISCUSSION

GHB and GBL have become popular party drugs. In the Netherlands, other countries in Europe, Australia and the USA there is an alarming increasing trend in the abuse of GHB and GBL.[7] The effects of GHB are dose dependent: excitatory in low doses and inhibitory in high doses.[13] GBL is a precursor of GHB, more easily accessible and also more dangerous than GHB, because its rapid absorption and increased bioavailability due to more lipophilic properties compared to GHB.[14] Incidental abuse of GHB can cause a nonintentional GHB intoxication, which results in life threatening complications and hospitalization.[22] In addition, GHB is heavily addictive and relapse rates are high.[6] Increasing incidents at hospital emergency units involving GHB and GBL intoxication and withdrawal have shown that the current medical care is inadequate to prevent complex, life threatening complications with aggressive and unpredictable behaviour.[6,7]

In the media GHB and GBL have received a lot of negative attention, because they are associated with date rape.[8] However, there are no data on the prevalence of DFSA, nor date rape under the influence of GHB or GBL.[29] Guidelines for prevention of DFSA include real-time, sensitive, and selective detection methods of date rape drugs.[8,9]

BODIPY sensors are developed to indicate the presence of GHB and GBL with a different mechanism of action involving the formation of hydrogen bonds.[31,34,9] We tested the BODIPY sensor GHB Orange and found that it is not an appropriate GHB detection test in the party scene. GHB Orange has several limitations as a real-time drug test. Firstly, the solubility of the BODIPY dye in aqueous solutions, which is enhanced by a polar solvent such as DMSO. Secondly, the fact that GHB Orange is not a specific test for detection of GHB, since it shows the same visible reaction in combination with sodium acetate (CH_3COONa) and hydrochloric acid (HCl). Thirdly, the pH-sensitivity of the BODIPY dye, which shows a reversible reaction after the addition of sodium hydroxide (NaOH). Considering these limitations, GHB Orange is not a reliable drug detection test.

In conclusion, further research on BODIPY dyes as fluorescent sensors for drugs, such as GHB and GBL is warranted. However, the usage of these drugs to facilitate rape will not be tempered by the introduction of drug detection tests such as GHB Orange and Green Date. Education and guidance by medical health professionals and parents is the mainstay of prevention of DFSA. Adolescents and young adults should be informed of the dangers of DFSA and specifically GHB.[30,8] Apart from date rape, GHB and GBL are dangerous substances, considering the rapid development of dependence, potential life threatening complications of intoxication and withdrawal, and high relapse rates.[21,6]

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Compliance with Ehtical Standards

Conflicts of interest

A.T.E. Veerman and S.R.T. Veerman report no financial relationships with commercial interests.

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